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TUBERCULOSIS AND PARASITISM AS CAUSES OF ABDOMINAL PAIN IN KOREAN PATIENTS

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DURING recent military campaigns in the Far East, American physicians treated large numbers of native Korean patients. Abdominal pain in the Korean as compared to the Occidental required a different interpretation. Intestinal parasites caused complications hitherto little thought of in the preoperative, operative and postoperative course of the surgical patient. At a large American military hospital in South Korea there was an excellent opportunity to study these problems. The majority of patients admitted were South Korean men of military age. An analysis of this group points out significant distinctive features in the diagnosis and treatment of abdominal pain in a Korean population.

PECULIAR CAUSES OF ABDOMINAL PAIN

Intestinal Parasites

During 1953 many patients were admitted to the hospital with the chief complaint of severe abdominal pain. There were the usual groups with gastroenteritis, appendicitis, cholecystitis, peptic ulcer and genitourinary disease. Thirty-nine patients, however, presenting a similar clinical picture were diagnostic problems.

These patients gave a history of recurrent bouts of intense epigastric pain, associated with repeated retching or vomiting. The pain, which began suddenly, occurred several hours after meals or during the night. Most of this group believed they were suffering from "chedda," a Korean word meaning vegetable poisoning. (The native South Korean doctors describe "chedda" as a syndrome of intermittent abdominal colic, nausea, vomiting and diarrhea developing days to weeks after the so-called poisoned vegetables have been eaten.) The most prominent physical finding was diffuse abdominal tenderness, with exquisite pain on pressure over the epigastrium. Rebound tenderness and muscle spasm localized to the epigastrium were frequent. Bowel sounds were normal or diminished, but never absent. White-cell counts varied from 6000 to 13,000, with 3 to 40 per cent eosinophils in the peripheral blood smear. Anemia of a hypochromic mycrocytic variety was noted in a third of the group. Gastric analyses showed a wide range of acidity. Because of the suspicion that a viscus had been perforated plain roentgenograms of the abdomen were taken. No free air was seen. Stool examinations on these patients showed large numbers of parasitic ova (Table 1).

The diagnosis of intestinal parasitism as the etiology of abdominal pain was made only after satisfaction of two basic criteria: exhaustive study, including gastrointestinal x-ray examination, had ruled out other diseases; and appropriate antihelminthic drugs had relieved the symptoms. Conversely, in a patient with chronic abdominal pain suggesting serious disease, deworming often eliminated some of the vague symptoms and clarified the diagnosis. Good results in the treatment of infestation with ascaris, ancylostoma and trichuris were obtained with a course of hexylresorcinol, followed by tetrachlorethylene. This was repeated if necessary. Six patients' stools contained ova of the Old World hookworm *(A. duodenale)* as the only parasite. In 2 only ascaris ova were seen. The clinical pictures in these two groups were similar, ancylostoma generally producing the more severe illness. The majority of the patients' stools contained at least two varieties of ova, usually hookworm and ascaris, so that in a particular patient it was difficult to establish which parasite was the basis of the abdominal pain. From studies of the dietary and hygiene habits of these patients it was concluded that in most cases "chedda," the so-called vegetable poisoning, was actually due to ingestion of mature filariform larvae of *A. duodenale* on the surface of contaminated unwashed vegetables. These larvae develop into adults in the duodenum and bite into the mucosa. The oral route of infection in hookworm disease is in contrast to the more common route in which the larvae penetrate the soft tissues of the bare foot.

There is little wonder at the enormous number of parasitic infestations seen in Koreans since the native Korean diet consists of raw or poorly cooked seafood, rice and vegetables grown in fields fertilized with human excreta. Most of the farm population work

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without shoes. Polluted water is drunk. Captain W. L. Stone[1] found during a study of 229 consecutive Korean patients at Taejon that only 1 patient's stools were free of parasites. In his series patients rarely harbored only 1 variety, and in a few the stools contained 5 varieties of ova. Fifty-seven per cent of the patients harbored *T. trichiura, A. duodenale* and *A. lumbricoides* together, and almost 87 per cent had at least 2 of these parasites.

Tuberculous Colitis and Peritonitis

In common with other underprivileged peoples living in war-ravaged lands the population of Korea suffers from a prevalence of tuberculosis in every form. Of 566 consecutive Korean patients given skin tests with serial dilutions of old tuberculin by Stone[1]

TABLE 1. *Varieties of Parasitic Ova in the Stools of 39 Korean Patients with Acute Abdominal Pain.*

PARASITE	PATIENTS HARBORING PARASITE	PERCENTAGE OF ALL PATIENTS
Trichuris trichiura	31	79%
Ancylostoma duodenale	27	69
Ascaris lumbricoides	26	67
Clonorchis sinensis	8	21
Strongyloides stercoralis	2	5
Unclassified ova	2	5
Endamoeba histolytica	1	2.5

93.3 per cent were positive. During the year studied 4 patients were seen on the surgical service with acute abdominal pain caused by intestinal or peritoneal tuberculosis.

The first patient was a twenty-two-year-old North Korean prisoner of war, who was admitted to the hospital on April 8, 1953, with a three-day history of generalized abdominal colic, nausea, vomiting and increasing distention. There was no past history of cough, hemoptysis, weight loss or abdominal distress. The temperature was 100°F., and the white-cell count 5300. X-ray films taken in the flat and upright positions showed gas and fluid levels in the small bowel. Operation was performed after forty-eight hours of decompression with a small-bowel tube. When the abdomen was opened 1 liter of milky fluid escaped. The intestinal serosa was studded with thousands of small and large tubercles, many caseous. There were multiple encysted pockets of fluid between fibrinous and fibrous adhesions. Several loops of small bowel were almost completely obstructed by firm adhesions, composed histologically of tuberculous granulation tissue. The obstructing bands were cut, and the wound was closed. The postoperative course was uneventful. He recovered after a long course of streptomycin and para-amino-salicylic acid. A primary focus of tuberculosis was not discovered.

The second patient, a twenty-year-old Korean laborer, entered the hospital with the clinical picture of an acute condition within the abdomen. At laparotomy tuberculous peritonitis was found. A third patient was admitted to a forward area Republic of Korea mobile surgical hospital with signs and symptoms of acute appendicitis. At operation tuberculous peritonitis with involvement of the appendix was discovered. An appendectomy was performed. Two days after operation he was evacuated south to Taejon. He died of tuberculous meningitis on the fourteenth day after operation. A fourth patient, with sudden onset of continuous abdominal pain and a boardlike abdomen, was explored at Taejon. Tuberculous colitis with a perforation of the cecum was found. The perforation was closed, and the patient recovered.

Carbarsone Reactions

Excruciating continuous abdominal pain frequently occurred during the course of carbarsone therapy for amebic hepatitis or colitis. These patients complained of burning epigastric pain. They presented a clinical picture very much like that of acute pancreatitis. Urinary diastase and blood amylase values were normal. This form of arsenical toxicity, causing smooth-muscle spasm, was relieved by regular doses of atropine.

Surgical Treatment of the Korean Patient

The clinical picture of disease due to the more frequent acute conditions of the abdomen was generally similar to that in the American patients. No great reliance, however, could be placed on the white-cell count of the peripheral blood as an indication of an acute surgical condition within the abdomen. At least a third of the patients with acute appendicitis, proved at laparotomy, had a normal or low white-cell count. This was particularly true in those on the tuberculosis wards in whom appendicitis developed.

The adult Korean who had survived malnutrition, cold and tuberculosis was strong, muscular and sturdy. He had been toughened by daily heavy manual labor and was accustomed to extremes of temperature. His daily meal, eaten without variety three times a day, consisted of two dishes: a bowl of salty brown soup made from fish, squid or octopus, and a bowl of boiled rice with small amounts of beans, turnips, fish or meat added. Cabbage, potatoes, pressed dehydrated seaweed, fruits, fresh meat and fish were expensive delicacies. There were no facilities for refrigeration at the usual Korean market. Fish and meat were offered for sale, on an open counter, day after day until partially decomposed. Fish heavily infested with fluke was eaten raw in many native dishes. Despite this sparse and unvaried diet there were few cases of frank vitamin, mineral or protein deficiency. There were, however, many cases of chronic anemia that were due to loss of blood from intestinal parasites.

A. lumbricoides caused considerable trouble in preoperative preparation. In most cases gastric or longer intestinal tubes became the nesting place for an adult ascaris worm within twelve hours of insertion, and the tube would have to be replaced. As a result the Miller–Abbott and Harris tubes were abandoned in favor of shorter tubes with larger lumens.

In the operating room the large numbers of adult round worms *(A. lumbricoides)* caused many difficulties. The anesthetist inserting his endotracheal tube occasionally met the round worms wiggling about in the pharynx. A dozen or more worms balled up into an obstructive bolus in the small bowel. At laparotomy this mass, palpated through the wall of the intestine, was easily mistaken for an intraluminal neoplasm. Several worms were usually found free in the peritoneal cavity after perforating shell-fragment or bullet wounds of the bowel. It was necessary to search for and remove these worms as part of the peritoneal toilet. Ova and small adults, hidden between loops of bowel, were undoubtedly left behind but caused no postoperative difficulty. It was concluded that the ova and worms died from lack of nutrition and were encysted in fibrous tissue.

Discussion

Abdominal syndromes due to parasitic diseases have become of increased interest and importance to the physician in the United States as well as to the medical officer stationed with troops in endemic areas. The massive population movements associated with military or political upheavals have spread once localized parasitic diseases to new geographic areas. Of every 15 United States servicemen returning from the Pacific area 1 was infested with the Old World hookworm, *A. duodenale*.[2] *C. sinensis* infestations have been seen in Chinese patients living in New York City.[3]

Patients with occult ancylostomiasis and sufficient acute abdominal findings to warrant laparotomy have been described.[4-6] Four of McEwan's[5] 12 patients were mistakenly operated on for appendicitis. Monat and Cooper,[7] Yenikomshian and Shehadi[8] and Zinneman[9] have recorded cases in which the history, physical examination and barium x-ray studies were first regarded as typical of duodenal ulcer. Denhoff,[10] reporting from New Guinea, concluded that incapacitating abdominal symptoms associated with a high degree of eosinophilia usually meant helminthic infestation. He urged caution in labeling patients with multiple abdominal complaints as psychoneurotic before helminthic infestation had been ruled out. Heartburn, epigastric pain relieved by bulky food or clay, constipation, diarrhea[11] and, rarely, bloody diarrhea[12-14] have been noted in patients with ancylostomiasis. Because hookworm ova may not appear in the stool until weeks after onset of symptoms, the diagnosis of ancylostomiasis is at times difficult to establish. An initial direct stool examination was positive in only 1 of 5 patients with hookworm in an Army hospital in Burma; concentration methods and repeated stool examinations for ova and parasites were necessary.[15] Blount's[14] patient was a boy with vomiting, epigastric pain and bloody diarrhea on the thirty-fourth day after exposure. Hookworm ova did not appear in the stool until the fifty-fifth day.

In most of the 39 Korean patients the acute symptoms followed ingestion of hookworm larvae on the surface of unwashed, uncooked foods. Craig and Faust,[11] Conn[16] and Pullen[17] also observed direct mouth infection in hookworm disease. Schapiro and Schapiro[18] noted the effects of wars in Spain, France, Ethiopia and the Far East in relation to parasitic diseases. Hunger, starvation and malnutrition caused men to eat garbage, rodents or other contaminated foods.

Belding[12] and others[11,17,19] have described specific lesions as the cause of abdominal pain in hookworm disease. Erosion and ulceration develop at the site of attachment of each worm, and abandoned sites bleed or by secondary infection become small pyogenic ulcers.

Intermittent colicky abdominal pain and tenderness are the commonest findings in ascariasis.[20-23] de Rivas[24] pointed out that of all patients infested with round worms 40 per cent have been subject to needless operations. Abdominal pain in ascariasis is due to intestinal obstruction in some cases and in others to nibbling on the small-bowel mucosa by ascaris. Minute ulcers are produced that are subsequently infected and may perforate.[17,19,20] Belding[12] concluded that the ascaris caused toxic and mechanical irritation of the bowel that resulted in intestinal spasm and colicky abdominal pain.

T. trichiura, the whip worm, is usually a benign parasite. In massive infestations there may be a clinical picture similar to hookworm disease, with nausea, vomiting, colic and epigastric tenderness.[25] The whiplike anterior portion of the worm imbedded in the intestinal mucosa stimulates an inflammatory reaction. This rarely develops into a pyogenic ulcer that perforates.[12]

Infestation with the Chinese liver fluke, *C. sinensis*, is manifested by chronic indigestion, hepatomegaly and cirrhosis. Many native Korean dishes call for fillets of raw fish. The metacercariae are encysted in the flesh of the fresh-water fish. After digestion of the fish, the freed parasites swim through the ampulla of Vater up into the bile ducts. During 1953 heavy clonorchis infestation presenting a clinical picture similar to that of obstructive jaundice requiring surgical correction was encountered in 3 patients. Laparotomy was necessary to establish the diagnosis in 1 of these.

Summary and Conclusions

In Korean patients there is an increased frequency of tuberculosis, a prevalence of tropical diseases as

malaria and amebiasis, and an almost universal infestation with intestinal parasites. Ascariasis particularly complicates the management of surgical patients. Heavy infestations of intestinal parasites may be manifested by a clinical picture similar to that of the acute abdominal emergencies requiring laparotomy.

Thirty-nine Korean patients with sudden severe abdominal colic, nausea, vomiting and epigastric tenderness were found to have large numbers of round worm *(Ascaris lumbricoides)*, Old World hookworm *(Ancylostoma duodenale)* and whip worm *(Trichuris trichiura)* ova in their stools. Most of these patients had recently ingested unwashed vegetables grown in fields fertilized with human excreta. Ingestion of ancylostoma larvae as surface contaminants of vegetables produces the most severe abdominal symptoms. Ascariasis with abdominal pain cannot be distinguished from ancylostomiasis. The diagnosis of parasitic disease as the cause of abdominal pain is established by the clinical picture, stool examination and relief of symptoms with antihelminthic drugs.

Infestation with the Chinese liver fluke, *Clonorchis sinensis*, may resemble obstructive jaundice. Carbarsone reactions mimic the acute abdominal catastrophe.

Needless laparotomy can be avoided by recognition of these abdominal syndromes.

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RENAL IMPAIRMENT DUE TO SARCOID INFILTRATION OF THE KIDNEY*

Report of a Case Proved by Renal Biopsies before and after Treatment with Cortisone

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IT is well known that sarcoid can involve many organs. At autopsy it is not rare to find infiltration of the kidneys,[1] but this is usually quite minimal in degree. Clinical renal insufficiency may occur in patients with sarcoidosis, but it is usually due to hypercalcemia and nephrocalcinosis[2] and not to involvement of the kidneys by the sarcoid process itself. There have been, in addition, a few reports of patients with sarcoidosis and renal failure in whom the renal lesion proved to be the result of other, probably unrelated processes. This report concerns a patient with generalized sarcoidosis and clinical signs of renal damage who did not have hypercalcemia and in whom renal biopsy revealed extensive sarcoid infiltration and no changes attributable to any other disease. A search through the literature reveals no other cases of this sort.

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Case Report

A 37-year-old Negro laborer (M.M.H. 368865), a native of the British West Indies, entered the hospital on August 25, 1953, with chief complaints of weakness and fatigue.

Four months previously excessive fatigue had been noted. Two months later there were weakness, dyspnea and palpitation on exertion. Subsequently, a transient swelling of the right wrist, associated with fleeting arthralgia and bone pains in the arms and legs, occurred. A rash on the extensor surfaces of both elbows and wrists became noticeable at this time. One week before admission he was forced to stop work because of malaise and weakness. At this time he noted occasional night sweats, with minimal cough and whitish sputum. He had lost a total of 23 pounds in weight during the 4 months before admission. There had been no urinary symptoms of any sort and no other significant symptoms referable to any other system.

Physical examination showed a well developed and well nourished man who did not appear particularly ill. Positive physical findings included generalized lymphadenopathy,

with soft and nontender lymph nodes 0.5 to 1 cm. in diameter, mild conjunctivitis without definite iritis and pigmented, raised skin lesions 2 to 4 mm. in diameter, scattered over the extensor surfaces of the elbows and knees.

The temperature was about 100°F. by rectum, and the blood pressure 124/80. All subsequent blood-pressure readings were within normal limits.

Examination of the blood revealed a hemoglobin of 15.5 gm. per 100 cc., with a sedimentation rate of 40 mm. per hour, and a white-cell count of 9750, with 66 per cent neutrophils, 25 per cent lymphocytes, 8 per cent monocytes and 1 per cent eosinophils. The blood Hinton test was negative. The serum albumin was 3.1 gm., the globulin 4.5 gm., the phosphorus 4.4 mg. and the alkaline phosphatase 5.1 Bodansky units per 100 cc. Two per cent of injected bromsulfalein dye was retained after 45 minutes. The serum sodium was 133 milliequiv., the potassium 4.6 milliequiv., the calcium 4.6 milliequiv., and the carbon dioxide content 23.8 milliequiv. per liter.

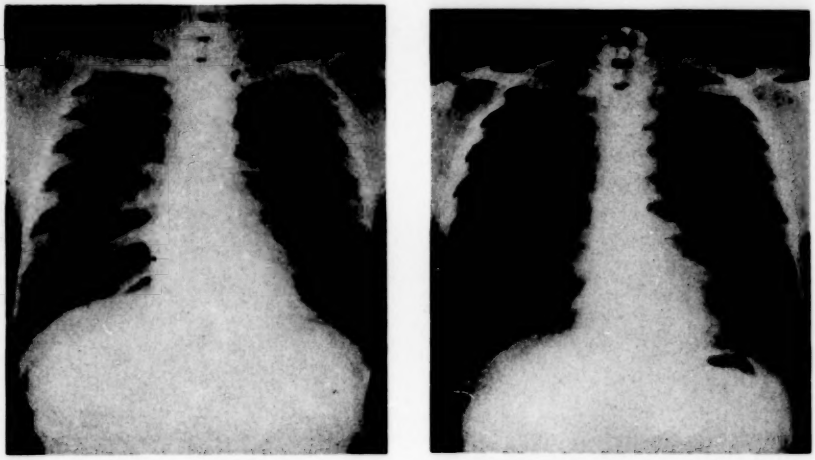
Two routine urinalyses disclosed a +++ test for albumin and a negative test for sugar. The sediment contained 5 to 10 white blood cells, 5 to 10 red blood cells and many hyaline and granular casts per high-power field. The blood nonprotein nitrogen was 75 and 66 mg. per 100 cc. on 2 occasions. The phenolsulfonphthalein test showed 9 per cent excretion of injected dye in 15 minutes and 26 per cent total in 2 hours. The serum creatinine was 1.9 mg. per 100 cc. (Borsook method, in which the normal value is less than 1.2 mg. per 100 cc.). Endogenous creatinine clearance was 68 cc. per minute, and total protein excretion in the urine was 1.08 gm. per day. Intravenous pyelograms showed very faint concentration of the dye, and the configuration of pelves and calyxes could not be seen. The kidneys were symmetrical and slightly increased in size; there were no stones or calcification.

Tuberculin skin tests with 1st-strength and 2d-strength PPD were negative. Material aspirated from the fasting stomach on 2 consecutive days was negative for acid-fast bacilli after concentration and smear; guinea-pig inoculation and culture of the gastric aspirations were also negative. X-ray study of the chest (Fig. 1*A*) initially demonstrated a fine, nodular infiltration scattered throughout both lung fields. The right hilus appeared somewhat accentuated. The heart was normal in size and configuration. X-ray examination of the hands and the large joints of the extremities showed no changes. On August 29 biopsy of a skin lesion over the elbow was performed, and the microscopical sections revealed large intradermal islands of epithelioid cell aggregates. No caseation or giant cells were seen, and few lymphocytes were noted. Acid-fast stains were negative.

On September 2, under local anesthesia, a small incision of the right flank was made, and the right kidney biopsied. Biopsies were also taken of the overlying muscle and fat.* The kidney surface appeared grossly normal. Sections of the tissues showed multiple small granulomas with marked involvement of the fat, moderate involvement of the muscle and marked involvement in the sections of the kidney (Fig. 2*A* and 2*B*). Dr. Sheldon C. Sommers, pathologist to the Massachusetts Memorial Hospitals, described the kidney sections as follows:

> The glomeruli are abnormal, with generalized moderate thickening of the capsular basement membranes and irregular thickening and hyaline appearance of the basement membranes in glomerular tufts. Epithelium of glomerular capsules is unusually prominent. The tubules contain a few colloid casts, and the proximal convoluted tubular cells have a coarse granular eosinophilic cytoplasm. Numerous interstitial granulomas are present, composed of large epithelioid macrophages with pink granular cytoplasm, abundant giant cells and moderate numbers of lymphocytes and eosinophils. Locally, the parenchyma is displaced and disrupted by the granulomatous inflammation. The blood vessels appear normal except for a mild hyaline thickening of some arterioles.

A periodic acid-Schiff stain of the sections (Fig. 3) confirmed the thickening of the basement membranes of the glomerulus and capsule and also revealed a fine reticulation and vacuolation of the intercapillary space. Acid-fast stains,



A B

FIGURE 1. *X-Ray Films of the Chest before* (A) *and Approximately Three Weeks after* (B) *Treatment with Cortisone, Showing Considerable Clearing in the Parenchymal Infiltration As Well As a Reduction in the Size of the Shadow in the Right Hilus.*

*Both kidney biopsies were done by Dr. C. R. Robertson. The details of the technic used and an account of its application in a series of patients with renal disease will be the subject of a later report.[3]

cultures and guinea-pig inoculation of renal tissue were negative for tubercle bacilli. Culture of the tissue was negative for other bacteria and for fungi.

On the day after the kidney biopsy a course of therapy with cortisone was started. The patient was given 200 mg. daily by mouth for 7 days and then 150 mg. daily for 17 more days. At the end of this time he was readmitted to the hospital for evaluation.

There had been great symptomatic and objective improvement in the disease during the interval. Appetite and strength were much improved, and he had gained 10 pounds. The skin lesions were fading, and the conjunctivitis had improved. The generalized lymphadenopathy had disappeared, and only a few small lymph nodes in the left axilla were palpable. An x-ray film of the chest (Fig. 1*B*) showed a definite reduction in the generalized nodular infiltration as well as a decrease in the markings in the right hilus.

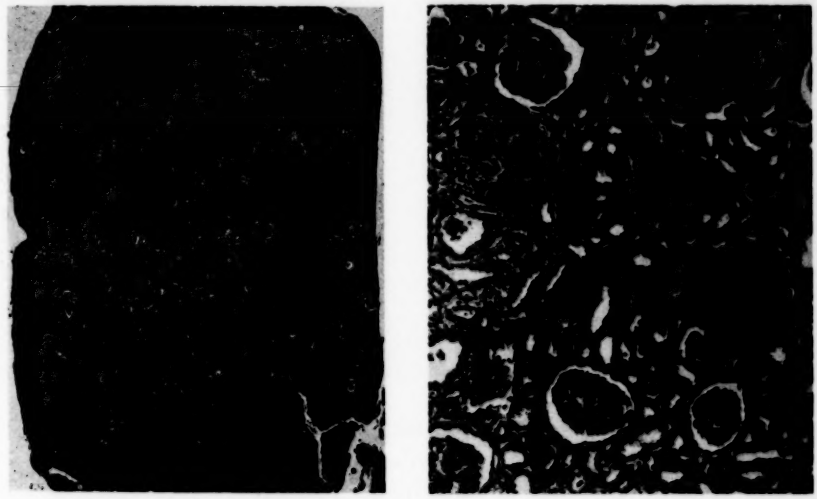
Table 1 summarizes the data pertaining to renal function and the urinary sediment. It is noted that on this readmission (October 1, Table 1), there was definite evidence of improvement in renal function. The spun urinary sediment contained no casts and only 1 or 2 white blood cells per high-power field. Qualitative tests for albumin on 2 random specimens of urine were negative, and a 24-hour collection contained a total of only 200 mg. of protein. The blood nonprotein nitrogen was 40 mg., and the serum creatinine 1.5 mg. per 100 cc. Endogenous creatinine clearance was 75 cc. per minute; phenolsulfonphthalein excretion measured 18 per cent in 15 minutes and 51 per cent in 2 hours.

On October 2 a 2d biopsy of the right kidney was carried out. There was no obvious change in the gross appearance of the renal cortex, and the microscopical appearance of the tissue sections was described by Dr. Sommers as follows:

> The appearance is unchanged from that observed on the previous biopsy. There are numerous interstitial granulomas composed of large eosinophilic epithelioid cells, abundant giant cells and smaller numbers of lymphocytes and eosinophils. As before, there is no necrosis. No inclusion bodies are seen. The tissue specimen contains more hyalinized atrophic glomeruli than was previously observed.

Other examinations of the renal tissue for tubercle bacilli, including culture, guinea-pig inoculation and acid-fast stains, were negative.

It was then decided to resume therapy with cortisone, and from October 3 to November 4, the patient received 150 mg. daily. During and immediately after this course of treatment he continued to improve symptomatically and was able to resume moderately heavy work without difficulty. Renal function progressively improved (Table 1). By December 3, approximately 1 month after the treatment had been stopped, the blood nonprotein nitrogen was 40 mg. and the serum creatinine 1.0 mg. per 100 cc., and endogenous creatinine clearance was 111 cc. per minute. Phenolsulfonphthalein excretion was 26 per cent in 15 minutes, the urinary sediment was entirely normal, and the total protein excretion measured less than 70 mg. a day.



A B

FIGURE 2. *Photomicrographs of First Kidney Biopsy.*
A=*low-power view (hematoxylin and eosin stain x12) of entire specimen. Note the diffuse and extensive infiltration (indicated by the light-staining areas) of the cortex.*
B=*higher magnification (hematoxylin and eosin x90), showing details of the granulomatous lesions and the hyaline changes in the glomeruli.*

During November and December qualitative tests for calcium in the urine with the Sulkowitch reagent were negative on 2 occasions, and a determination of serum calcium concentration on December 3 yielded a value of 4.8 milliequiv. per liter.

Without further therapy the patient's general condition gradually began to regress, and he once more complained of weight loss, fatigue and arthralgia. By February, 1954, there were definite signs of reactivation of the pathologic process, with the reappearance of skin lesions and generalized lymphadenopathy and a striking increase in the pulmonary infiltration seen on x-ray study. In February, and again in March, renal function appeared to be slightly reduced again (Table 1), and cylindruria and marked albuminuria had reappeared.

In April he was given another course of therapy, this time with hydrocortisone, 100 mg. daily for a total of 30 days. By the end of this time (April 29, Table 1) he had again

improved symptomatically and objectively. Urine-function tests were not significantly changed (Table 1), but albuminuria was greatly reduced.

Discussion

Schaumann[4] was the first to recognize sarcoidosis as a widespread systemic disease. At about the same time Kuznitzky and Bittorf[5] reported abnormalities in the urine of a patient they suspected of having sarcoidosis of the kidneys. In 1924 Schaumann[6] noted the presence of "a little albumen, casts and leucocytes" in the urine of a patient with "benign lymphogranulomatosis," but stated that "it remains to be seen if the kidneys can be invaded by benign lymphogranulomata." Nine years later he was able to report the presence of these lesions in the kidneys of one of his patients who had died of pulmonary insufficiency.[7]

Since that time the granulomas of sarcoidosis have occasionally been found in the kidney at autopsy. The prevalence of this lesion among patients with sarcoid is not high. Longcope and Freiman[1] observed renal granulomata in 4 of 30 autopsies. In a recent extensive review of all reported autopsies in sarcoidosis (except those of Longcope and Freiman), Branson and Park[8] reported the kidneys to be involved in only 8 of 117 cases. The degree of involvement may vary from the finding of a few scattered lesions in the cortex and medulla, which is the usual situation, to massive infiltration and destruction of renal tissue.

It is stated that a mild degree of albuminuria is not unusual in sarcoidosis, but in most cases this is not associated with other evidence of renal damage.[1] The few reported cases of renal insufficiency with sarcoid have been due largely to nephrocalcinosis and hypercalcemia. Sections of the kidneys do not always reveal the presence of sarcoid lesions,[9,10] indicating clearly that the renal damage is to be attributed to the disorder of calcium metabolism rather than directly to sarcoid infiltration. The cause of the calcium disorder in sarcoid is not known. A current hypothesis, proposed by Henneman, Carroll and Dempsey,[11] is that a disturbance in endogenous vitamin D metabolism results in a relative excess of this substance and increased absorption of calcium from

Figure 3. *Periodic Acid-Schiff Stain (X160), Showing Thickening of the Basement Membranes of the Glomerulus and Capsule.*

No granulomatous lesions are visible in this section.

Table 1. *Tests of Renal Function.*

Date	Blood Non-protein Nitrogen	Serum Creatinine	Endogenous Creatinine Clearance	Phenolsulphonphthalein Excretion at 15 min.	Phenolsulphonphthalein Excretion 2-hr. total	Total Urinary Protein Excretion	Urinary Sediment: White Blood Cells	Urinary Sediment: Red Blood Cells	Urinary Sediment: Casts
	mg./100 cc.	*mg./100 cc.*	*cc./min.*	%	%	*gm./day*	*per high-power field*	*per high-power field*	*per high-power field*
8/27/53	75	—	—	6	30	—	0-5	0-5	Many (granular & hyaline)
9/ 1/53*	66	1.9	68	9	26	1.08	5-10	5-10	Many (granular & hyaline)
9/10/53	52	0.9	52	15	43	—	—	—	—
10/ 1/53	40	1.5	75	18	51	0.20	1-2	0	0
12/ 3/53	40	1.0	111	26	—	<0.07	0	0	0
2/11/54	39	1.4	74	15	—	0.97	—	—	—
3/27/54†	43	1.6	79	19	55	2.20	0-5	0	Occasional (granular & hyaline)
4/29/54	25	1.3	86	23	68	0.27	0-1	0	Rare (granular)

*Cortisone given from 9/3/53 to 11/4/53.
†Hydrocortisone given from 4/1/54 to 4/30/54.

the intestines as well as increased mobilization of bone salts.

Several cases of renal damage in patients with sarcoidosis have been proved to be due to other lesions. In 1 of a series of cases of sarcoid reported by Ricker and Clark,[12] the patient died in uremia and was found to have renal arteritis and periarteritis, with sarcoid lesions in other organs only. Chronic glomerulonephritis[13,14] and chronic pyelonephritis with polycystic kidneys[15] have also been responsible for renal insufficiency in patients with sarcoid. Snapper[16] reports a case of sarcoidosis and diabetes mellitus in which renal insufficiency resulted from intercapillary glomerulosclerosis. Another patient with sarcoidosis and clinical renal failure, described by Horton, Lincoln and Pinner,[17] had tuberculous lesions in the kidney as well as some calcification of the tubules.

Rutishauser and Rywlin[18] discuss a patient with severe hypertensive vascular disease and uremia who died of a cerebrovascular accident. Autopsy revealed contracted kidneys, extensively infiltrated with a granulomatous process resembling sarcoid. Similar, but less severe, lesions were found in lymph nodes and other viscera. No data on calcium metabolism were presented. The authors suggest that sarcoidosis was the essential disease and was responsible for the hypertensive vascular disease and for the resulting nephrosclerosis. The alternative possibility — that the sarcoidosis was an incidental complication of preexisting vascular disease — cannot be ruled out. No other cases of this sort have been reported.

It is clear, therefore, that most patients with sarcoidosis who have renal insufficiency may be expected *not* to have renal sarcoidosis as the major cause of their difficulty. Klinefelter and Salley,[19] in an article entitled "Sarcoidosis Simulating Glomerulonephritis," could find, in a review of the literature in 1946, only 3 cases of renal insufficiency with sarcoidosis, and reported a fourth case of their own. These 4 cases included the patient of Horton, Lincoln and Pinner,[17] who showed renal tuberculosis and calcification, and that of Rotenberg and Guggenheim,[20] who was later autopsied and described by Parker[15] as having polycystic disease. The authors' own patient had hypercalcemia. The fourth case reviewed, originally reported by Salvesen,[21] was not supported by histologic examination and had no data on calcium metabolism.

In the case reported above, the diagnosis of sarcoidosis appears reasonably certain on the basis of the characteristic clinical involvement of eyes, lungs, lymph nodes and skin, the relatively benign clinical course and the response of the disease to therapy with cortisone. The noncaseating granulomatous lesions found in the skin, muscle, perirenal fat and kidneys were in all ways typical of sarcoidosis. Tuberculosis seems to be excluded by negative tuberculin skin tests and negative studies for acid-fast bacilli in sputum, gastric washings and tissue specimens. Negative cultures also appear to exclude other bacterial or mycotic pathogens.

At the time of the first admission to the hospital, the evidence of renal damage was prominent. The renal-function data (Table 1) revealed a moderately severe degree of glomerular and tubular damage. Several normal serum calcium determinations and negative calcium tests of the urine indicated that a disturbance of calcium metabolism was unlikely, and this was supported by the absence of calcium stones and renal calcification in the pyelograms.

Solely from the point of view of the renal disorder, the clinical picture might have been compatible with moderately advanced chronic glomerulonephritis or with latent pyelonephritis, either of which had not yet produced hypertensive vascular disease and had not yet started to contract or deform the renal structure. However, the renal-biopsy material contained no evidences of either of these diseases, and instead, showed extensive infiltration with the granulomas of sarcoid, as well as thickening and hyaline changes in glomerular tufts. The latter lesions were not as severe as those described by Teilum[22] in a patient with sarcoidosis, who did not have any granulomatous infiltration of the kidney. Teilum suggests that hyalinosis of vascular membranes may be a characteristic change produced by sarcoidosis, in common with other "hyperglobulinotic" diseases such as disseminated lupus. Regardless of the validity of this hypothesis, it appears most reasonable in the present case to consider the membrane changes in some way related to the sarcoid process, and to conclude that sarcoidosis was the direct cause of the clinical evidence of renal damage.

The patient's general response to therapy with cortisone was striking and was like that reported by other workers.[9,23] The skin and eye lesions, as well as the enlarged lymph nodes rapidly disappeared, and the x-ray films of the chest indicated similar improvement in the pulmonary lesions (Fig. 1*A* and *B*). There appeared to be slight but definite increase in glomerular and tubular function of the kidneys associated with the therapy and also a great reduction in the excretion of albumin and casts (Table 1). That all these clinical and physiologic changes were in fact related to therapy was strongly suggested by the recurrence of the original signs and symptoms and the return of albuminuria two or three months after the end of the first course of treatment, as well as by the second remission of the signs of disease after the treatment with hydrocortisone.

Despite the clinical changes the second renal biopsy, taken when renal function appeared to be much improved, failed to reveal any significant change in the lesions. The increases in renal function may have been due, therefore, to a nonspecific, enhancing effect of cortisone on renal hemodynamics.[24] It is also possible that changes in renal structure responsible for

the improvement in function did occur but were too subtle to be detected by microscopical examination of a small section of routinely stained tissue. The apparent effect of adrenal steroids on albuminuria in this case is similar to that of ACTH in patients with the nephrotic syndrome,[25] and may be the result of changes in permeability of the glomerular membrane.

Summary

A case of generalized sarcoidosis that was distinguished by signs of moderate renal damage is reported. Renal biopsy revealed extensive sarcoid infiltration of the kidney, which did not improve after treatment with cortisone, despite transient clinical improvement in renal function and in the other signs of the disease.

A review of the literature emphasizes the rarity of sarcoid infiltration as a cause of clinical renal disease in patients with sarcoidosis, although minimal involvement of the kidney with granulomas is not an unusual autopsy finding. Most patients with renal insufficiency and sarcoidosis have hypercalcemia and nephrocalcinosis, or have other lesions of the kidney. None of these complications were present in this case.

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DYNAMICS OF THIOCYANATE DIALYSES*

The Artificial Kidney in the Therapy of Thiocyanate Intoxication

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THE thiocyanates have been used widely in the treatment of hypertension.[1] They produce a significant drop in blood pressure in about 50 per cent of patients, and they often succeed in controlling hypertensive headaches that are resistant to other forms of treatment.[2] A serious drawback to their use, however, has been the high frequency of serious toxic effects, some of which have been fatal.[3] It has been estimated that 14,000 pounds of this drug were consumed in the United States for medicinal purposes alone in 1952.[4] Its use in foreign countries is estimated to be even greater.

The toxic reactions to thiocyanate are numerous and difficult to anticipate. The reasons for this are twofold. In the first place there is a narrow range between effective therapeutic blood levels and levels that are toxic. In some persons these two values may be almost identical, and there is virtually no margin of safety between the toxic and therapeutically effective dose of thiocyanate.[5] Secondly, several studies have shown that there is a uniformly slow rate of renal excretion, which is the only important route of elimination.[5,6]

The thiocyanate concentration in the blood is a rough index of the total thiocyanate content of the body; therefore, most of the serious reactions to thiocyanate can be expected to occur with high blood levels. Blood levels above 14 mg. per 100 cc. are considered dangerous.[7] However, deaths from thiocyanate have occurred with levels as low as 3.3 mg. per 100 cc.[8]

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Current methods of treatment of thiocyanate poisoning, which consist of supportive measures aimed at maintenance of life until the drug can be excreted or metabolized, have occasioned considerable dissatisfaction because of their lack of specificity. Ideal therapy must be directed toward either more rapid removal or accelerated detoxification of the drug. Increasing the rate of detoxification is not easily accomplished, since the metabolic pathways are not known.* Increasing the rate of removal is the only course, and massive intravenous infusions have been administered to initiate diuresis. Even so, it may take days, and even weeks, to eliminate the ion from the body. It is during this period, after discontinuance of the drug and while the serum level is slowly decreasing, that most of the deaths attributable to thiocyanate poisoning occur.[11]

Because of the inadequacy of current therapy, it seemed advisable to test the efficacy of extracorporeal hemodialysis in removing thiocyanate from the body. This procedure recommended itself because of the following observations: thiocyanate, after injection, is almost totally distributed in the extracellular portion of the body fluids[12] (the quantity of thiocyanate in the plasma is believed to be in equilibrium with that in the interstitial space [12,13]); only a fraction (approximately a third) of the plasma thiocyanate is reversibly bound to protein and lipoid[13,14]; and the molecular weight of thiocyanate is 58, which is almost identical with urea, a substance known to be readily dialyzable. The observations reported below confirm the feasibility of hemodialysis in the treatment of thiocyanate intoxication.

Clinical Material

Five patients (S.S., F.W., F.R., W.R. and D.P.) with severe chronic renal disease without edema were selected for this study. The diagnoses were either glomerulonephritis or pyelonephritis with secondary hypertension and uremia. The group consisted of 4 men and 1 woman, and the ages ranged from twenty-two to forty-five. These patients were selectively admitted to the hospital for dialysis on the artificial kidney because of their renal disease.

Enteric-coated potassium thiocyanate† was administered orally in divided doses, ranging from 0.8 to 1.8 gm. per twenty-four hours. An attempt was made to attain thiocyanate blood levels of at least 10 mg. per 100 cc., and this necessitated giving the medication over a period of five to twelve days.

Two other patients, who on admission had high plasma levels of thiocyanate, were included in the study. One (L.D.), a fifty-seven-year-old woman, was admitted to the Closed Neuropsychiatric Section of Brooke Army Hospital because of suicidal behavior. In addition to her obvious psychosis, she had hypertension and moderate renal disease. A toxic psychosis was suspected when she was found to have a plasma thiocyanate level of 29.9 mg. per 100 cc. After dialysis on the artificial kidney, when the plasma thiocyanate level was lowered to 1.5 mg. per 100 cc., she made a complete symptomatic recovery.[15] The other patient (R.M.), a fifty-eight-year-old man with malignant hypertension and uremia, just before dialysis on the artificial kidney for the renal disease, was treated for hypertensive headaches with potassium thiocyanate.

Methods

The Kolff–Brigham artificial kidney, with the more recent improvements, was used in these studies. Previously outlined technics for the use of this apparatus were followed, and a minimum of technical difficulty was encountered.[16] Each patient was given 100 mg. of heparin through the venous cannula at the onset of dialysis and 10 mg. hourly throughout the procedure.

The dialyzing membrane was seamless cellophane tubing 1.82 cm. in diameter; an average of 4633 cm. with a surface area of 24,241 square cm. was used to wind the machine. Approximately 750 cc. of carefully crossmatched blood was used to prime the cellophane tubing. Dialysis time averaged six hours except for 2 cases, each of which averaged five hours. The blood flow through the machine, as measured by a flow meter, averaged 269 cc. per minute, with a range of 210 to 300 cc. per minute. During a six-hour dialysis, new baths were used at two-hour intervals as advocated by Wolf et al.[17] The concentrations of the bath constituents, which approximated those recommended by Merrill and his associates,[18] were as follows: sodium 140 milliequiv., potassium 4 milliequiv., calcium 2.6 milliequiv., magnesium 2.1 milliequiv., bicarbonate 27 milliequiv., and chloride 121.5 milliequiv. per liter, and glucose 200 mg. per 100 cc. Since most patients were dialyzed primarily because of uremia and acidosis, there were only slight variations of these "normal" bath concentrations. These variations were introduced in accordance with specific electrolyte determinations of the patient's plasma as measured on the day before dialysis.

Samples of blood and dialysate for the determination of thiocyanate were obtained at the beginning and end of each two-hour bath. In most patients blood and bath samplings were performed at more frequent intervals. By means of these values, the total quantity of thiocyanate removed could be compared with the depression in the serum thiocyanate level, and the dynamic constants of the dialysis could be computed. All blood specimens were obtained from the arterial cannula, and the dialysate samples were taken from the same representative portion of the bath.

The plasma concentrations of thiocyanate were

*Methylene blue, sodium thiosulfate and vitamin B_{12a} have been suggested as antidotes because of their specificity for cyanide,[9] which is one of the end products of thiocyanate metabolism.[10]

†Potassium thiocyanate, available as "Enseals" for oral administration from Eli Lilly and Company, Indianapolis, Indiana, was used exclusively throughout this study.

measured by the method of Barker[7] with the following modifications: the protein-free filtrate was separated by centrifugation, and the method was adapted to the Coleman junior spectrophotometer at a wave length of 550 microns. Bath and urinary thiocyanate determinations were made with the same modifications. Any thiocyanate or thiocyanatelike color found in the bath at zero time was subtracted from subsequent values. Regarding the urine, a thiocyanatelike color developed by ferric nitrate is found in all subjects regardless of the presence or absence of thiocyanate.[8,19] Before administration of the drug, this value was ascertained and subtracted from subsequent values. Urea was determined by the urease-aeration method of Van Slyke and Cullen.[20]

Just before dialysis, the renal clearances of thiocyanate and urea were determined on 2 patients (S.S. and W.R.). Thiocyanate clearances were also measured on 2 normal subjects. These studies were performed by means of a multiperforated catheter inserted into the bladder. When a urinary flow of 2 cc. per minute was obtained, accurately timed blood and urine samples were collected. The bladder was carefully emptied at the time of collection after sterile saline solution and air had been instilled. Urea and thiocyanate clearances were obtained with the use of the following conventional expression:

$$(1)\quad C = \frac{UV}{P}$$

C = cc. of plasma cleared per minute
U = concentration in urine in mg./cc.
V = flow in cc. per minute
P = concentration in plasma mg./cc.

The dialysance of thiocyanate (a quantity that, for the artificial kidney, is analogous to clearance for the biologic kidney) was determined by the formula proposed by Wolf et al.[17]:

$$(2)\quad D = \frac{U \times u}{P - U}$$

where

D = cc. of plasma dialyzed (cleared) per minute
u = dialysate volume of artificial kidney (100,000 cc.) divided by elapsed dialysis time (B/t—see below)
U = dialysate concentration of thiocyanate expressed in mg./cc.
A = plasma concentration of thiocyanate expressed in mg./cc.

When the clearance formula (1) is compared with the dialysance formula (2), it is seen that:

u x U is substituted for UV and represents rate of excretion of thiocyanate into bath;
P − U is substituted for P and represents plasma level corrected by quantity of thiocyanate that has accumulated in bath — in other words, plasma-bath gradient.

For the method of calculation used in this study, the dialysance formula is better restated as:

$$(3)\quad D = \frac{dE'}{dt} \Big/ \frac{}{P - U}$$

where $\frac{dE'}{dt}$ represents the *instantaneous* rate of excretion of thiocyanate into the bath as calculated from tangents drawn to the cumulative graph of thiocyanate in the bath (Fig. 1). The tangents were drawn with an optical device that permitted an accuracy of the same order of magnitude as the scale of the graph itself.[21] The dialysance, calculated from either (2) or (3), is characteristic for different molecular or

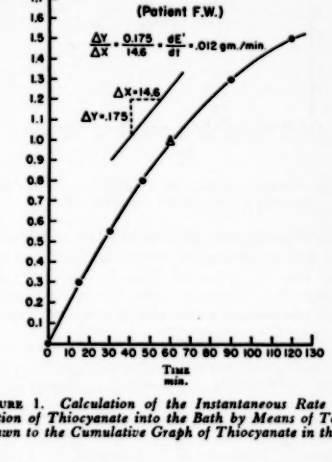

FIGURE 1. *Calculation of the Instantaneous Rate of Excretion of Thiocyanate into the Bath by Means of Tangents Drawn to the Cumulative Graph of Thiocyanate in the Bath.*

ionic species, but for any one species it varies roughly with the rate of blood flow and the total dialyzing surface area.[17] The dialysance should remain relatively constant during any one procedure, provided the blood flow is carefully controlled throughout the run.

From the data obtained during a clinical dialysis, the average dialysance ($\bar{D}$), and the rate of decrease per unit time of the plasma-bath concentration gradient (β), may be computed. These values, together with the volume of the dialysate (B) may be used to calculate the volume of distribution (b) for thiocyanate by means of the formula first proposed by Wolf et al.[17]:

$$(4)\quad \beta = \frac{B+b}{B} \cdot \frac{\bar{D}}{b}$$

or upon solution for b

$$(4')\quad b = \frac{B\bar{D}}{\beta B - \bar{D}}$$

In the discussion to follow, the term *volume of distribution* is taken to mean the total fluid volume in which diffusible thiocyanate is distributed within the body. This calculation is based on the conventional assumption that thiocyanate is found everywhere at the same concentration as it is found in the plasma. A more obvious method by which the volume of distribution may be calculated than the one presented in this paper is to divide the difference between initial and final plasma levels into the total amount recovered in the bath. However, as may be seen from Figure 2, the initial plasma level is not a reliable one to use since the patient-bath system has not yet reached equilibrium. Further on in the dialysis, plasma levels fall along a logarithmic straight line and hence are more reasonable values to use in the calculations. Even these latter points do not sit on the line perfectly, however, because of the usual experimental fluctuation. The most reasonable approach is to use an "average plasma line" determined from all the relevant plasma levels. This is exactly what is implied by formula (4) given above. The slope of the plasma-bath gradient line is fitted by the method of least squares.[22] Even though the volume of distribution can be roughly calculated by means of the differences of plasma levels and bath recoveries, the method presented here should produce a more reliable estimate of these volumes.

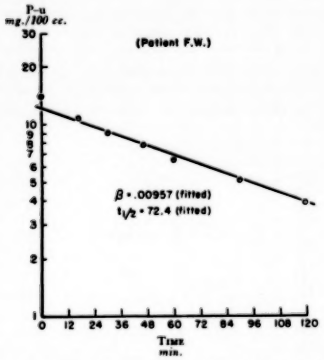

FIGURE 2. *Rate of Decrease per Unit of Time of the Plasma-Bath Concentration Gradient* (β).

RESULTS

Reduction of Plasma Thiocyanate Levels and the Recovery of Thiocyanate by Dialysis

Elevated serum thiocyanate levels were progressively reduced in 7 patients who underwent hemodialysis on the artificial kidney (Table 1). The most noticeable changes occurred during the first two hours (Bath 1). In some cases more frequent sampling revealed that the greatest reduction of serum thiocyanate occurred during the first fifteen minutes of each dialysis (Table 2). The highest serum thiocyanate level, 24.8 mg. per 100 cc., was lowered to 1.5 mg. during a six-hour run, and the lowest level, 7.3 mg. per 100 cc., was reduced to 1.3 mg. (Table 1).

The percentage decrease of the initial serum thiocyanate level was quite constant in all patients for each two-hour dialysis, even though the serum thiocyanate values differed considerably from patient to patient (Table 3). During the first two hours, the initial level fell an average of 58.8 per cent, with a range of 45.6 to 68.5 per cent. After four hours, the initial level was reduced an average of 79.4 per cent, with a range of 68.5 to 86.0 per cent. After six hours, the average decrease was 87.5 per cent. The average percentage drop in 2 patients who were dialyzed for only five hours was 86.8 per cent. Thus, the five-hour dialyses compared very favorably with the six-hour dialyses.

As was expected from the observations on the plasma levels given above, the accumulation of thiocyanate in the dialysate was most striking during the first two hours (Table 1). More frequent sampling revealed that the greatest quantity of thiocyanate re-

TABLE 1. *Removal of Thiocyanate from 6 Patients Dialyzed on the Artificial Kidney.**

Dialysis Time	Patient L.D.		Patient S.S.		Patient F.W.		Patient F.R.		Patient W.R.		Patient D.P.		Average	
	Plasma Level	Dialysate Recovery†	Plasma Level	Dialysate Recovery†	Plasma Level	Dialysate Recovery†	Plasma Level	Dialysate Recovery†	Plasma Level	Dialysate Recovery†	Plasma Level	Dialysate Recovery†	Plasma Level	Dialysate Recovery†
hr.	*mg./100 cc.*	*mg.*	*mg./100 cc.*	*mg.*	*mg./100 cc.*	*mg.*	*mg./100 cc.*	*mg.*	*mg./100 cc.*	*mg.*	*mg./100 cc.*	*mg.*	*mg./100 cc.*	*mg.*
0	24.8	—	18.5	—	14.1	—	13.8	—	7.3	—	12.2	—	15.1	—
2	7.8	2000	7.5	2850	5.4	1500	6.0	1800	3.9	750	4.8	1380	5.9	1713
4	3.5	700	3.4	1400	2.3	700	3.5	800	2.3	530	2.2	690	2.9	803
6	1.5	400	2.3	600	1.6‡	200‡	2.1‡	360‡	1.3	350	1.5	670	1.7	430
Total dialysate recovery		3100		4850		2400‡		2960‡		1630		2740		2946

*Another patient, R.M., had plasma thiocyanate level of 15.1 mg./100 cc. lowered to 1.7 mg./100 cc. in 6 hr. Dialysate recovery not measured.
†Values indicate recovery during preceding 2 hr.
‡Dialysis time for last bath 1 hr.

moved during a two-hour dialysis was 2.85 gm. in patient S. S., whose serum thiocyanate level was 18.5 mg. per 100 cc. initially and 7.5 mg. per 100 cc. two hours later. The total of 4.85 gm. over a six-hour period was greater than any other recovery in this series. The smallest quantity removed during a two-hour dialysis was 0.75 gm. in patient W.R., whose initial serum level was 7.3 mg., and whose two-hour level was 3.8 mg. per 100 cc.

Of the total quantity of thiocyanate removed during a six-hour dialysis, an average of 57.2 per cent was removed during the first two hours (Bath 1), which was somewhat better than half the thiocyanate recovered at the end of six hours (Table 4). During the third and fourth hours (Bath 2), 27.5 per cent and during the final two hours (Bath 3) 15.3 per cent was removed. In the 2 patients whose dialysis time was only five hours, the average removal during the fifth hour was only 10.2 per cent.

Comparison of Renal Clearance with Dialysance of Thiocyanate

The renal clearance of thiocyanate as determined in 2 patients with chronic renal disease was 0.76 and 1.77 cc. per minute (Table 5). Their urea clearances expressed as percentage of normal were 12.7 and 7.6 respectively. Thiocyanate clearances in 2 normal subjects were 1.6 and 2.7 cc. per minute, comparing favorably with the average of 2.3 cc. per minute recorded in the literature (Table 6).

The dialysance of thiocyanate in 5 patients during the first two hours of dialysis (Bath 1) averaged 174.0 cc. per minute, with a range of 135.7 to 211.9 cc. per minute (Table 7). The average dialysance for the third and fourth hours (Bath 2) averaged 178.5 cc. per minute (Table 8). Dialysances for the first two baths calculated for each patient did not vary from one another more than 10 per cent in the average. The dialysance of urea averaged 200.6 and 222.7 cc.

TABLE 2. *Dynamics of Thiocyanate Removal with the Artificial Kidney* in F. W., a Forty-Three-Year-Old Woman with Chronic Glomerulonephritis.*

BATH	TIME	PLASMA LEVEL P	RECOVERY IN DIALYSATE u	P-u	INSTANTANEOUS EXCRETION INTO BATH	DIALYSANCE†	AVERAGE BLOOD FLOW
	min.	*mg./100 cc.*	*mg./100 cc.*	*mg./100 cc.*	*gm./min.*	*cc./min.*	*cc./min.*
	0	14.1	—	14.1	0.0208	147.7	
	15	11.1	0.3	10.8	0.0183	169.6	250
	30	9.5	0.55	8.95	0.0156	174.6	
1	46	8.6	0.8	7.8	0.0145	185.6	255
	60	7.5	1.0	6.5	0.012	184.9	
	90	6.4	1.3	5.1	0.0089	174.4	275
	120	5.4	1.5	3.9	0.00585	150.0	
Average						169.5±15.3	260
	0	5.3	—	5.3	—	—	
	30	4.1	0.25	3.85	0.00593	154.0	275
2	60	3.3	0.5	2.8	0.005	178.6	
	90	2.6	0.6	2.0	0.0047	235.0	275
	120	2.3	0.7	1.6	0.00432	187.8	
Average						188.0±33.9	275
	0	2.3	—	2.3	—	—	
3	30	1.8	0.15	1.65	0.00315	190.9	250
	38	1.6	0.2	1.4	0.0023	164.3	300
Average						177.6±18.5	275

*Cellophane tubing: length, 4712 cm.; area 24,646 sq. cm.

†Calculated with formula: $\frac{dE'}{dt} \div P\text{-}u$ where $\frac{dE'}{dt}$ expressed in gm./min. & P-u in gm. per cc.

TABLE 3. *Reduction of Plasma Thiocyanate Level Expressed as Percentage of Initial Plasma Concentration.*

DIALYSIS TIME	PATIENT L.D. REDUCTION OF INITIAL LEVEL	PATIENT S.S. REDUCTION OF INITIAL LEVEL	PATIENT F.W. REDUCTION OF INITIAL LEVEL	PATIENT F.R. REDUCTION OF INITIAL LEVEL	PATIENT W.R. REDUCTION OF INITIAL LEVEL	PATIENT D.P. REDUCTION OF INITIAL LEVEL	AVERAGE REDUCTION*
hr.	%	%	%	%	%	%	%
0							
2	68.5	59.5	61.7	56.5	45.6	60.7	58.8±7.56
4	86.0	81.6	83.7	74.6	68.5	82.0	79.4±6.60
6	94.0	87.5	88.7†	84.8†	82.2	87.8	87.5±4.20

*±standard deviation.

†Dialysis time for last bath 1 hr.

per minute for the first and second baths respectively (Table 8).

Table 2 and Figure 1 show the methods and calculations that were used to determine the dialysance on patient F.W. They are representative of the method for calculating dialysances on other patients. Each bath was treated separately. The data from the first bath was more reliable than those from the other two since more frequent sampling was performed for this bath. There was a steady decrease in the plasma concentration of thiocyanate and concomitantly a rise in the amount of bath thiocyanate. Figure 1 is an arithmetic plot of the accumulation of thiocyanate versus time in Bath 1. A smooth line was drawn by means of a French curve so that all plotted points would be taken into consideration. Tangents were drawn to the curve at the specific times that coincided with the plasma and bath thiocyanate determinations. The slope of the tangents was determined graphically. The value thus obtained in grams per minute represents the instantaneous rate of removal of thiocyanate at the time in question and corresponds to the numerator U x u of the conventional equation:

$$(2)\quad D=\frac{U\times u}{P-U}$$

or to dE'/dt of the more exact equation:

$$(3)\quad D=\frac{dE'/dt}{P-U}$$

TABLE 4. *Thiocyanate Recovery Expressed as Percentage of Total Thiocyanate Removed.*

Dialysis Time	Patient L.D.		Patient S.S.		Patient F.W.		Patient F.R.		Patient W.R.		Patient D.P.		Average Recovery†
	Dialysate Recovery*	Total Recovery	Dialysate Recovery*	Total Recovery	Dialysate Recovery*	Total Recovery	Dialysate Recovery*	Total Recovery	Dialysate Recovery*	Total Recovery	Dialysate Recovery*	Total Recovery	
hr.	*mg.*	%	*mg.*	%	*mg.*	%	*mg.*	%	*mg.*	%	*mg.*	%	%
0													
2	2000	64.5	2850	58.7	1500	62.5	1800	60.8	750	46.0	1380	50.4	57.2±7.2
4	700	22.6	1400	28.9	700	29.2	800	27.0	530	32.5	690	25.2	27.5±3.4
6	400	12.9	600	12.4	200‡	8.3‡	360‡	12.2‡	350	21.5	670	24.4	15.3±6.2
Total dialysate recovery	3100	100	4850	100	2400‡	100	2960‡	100	1630	100	2740	100	100

*Values indicate recovery during preceding 2 hr.
†±standard difference.
‡Dialysis time for last bath 1 hr.

Since the plasma and bath values of thiocyanate concentration were determined simultaneously the denominator of equation (3) was easily obtained by subtraction of the respective values (Table 2).

TABLE 5. *Renal Clearances of Thiocyanate in 2 Patients with Chronic Renal Disease.*

Patient	Plasma Concentration	Average Plasma Concentration*	Urine Concentration†	Time	Average Urinary Flow‡	Renal Clearance§	Average Thiocyanate Clearance	Urea Clearance
	mg./cc.	*mg./cc.*	*mg./cc.*	*min.*	*cc./min.*	*cc./min.*	*cc./min.*	*% of normal*
S.S.	P_1 0.178	0.1765	0.0507	22.0	2.45	0.703	0.758	12.7
	P_2 —		0.0549	22.5	2.62	0.812		
	P_3 0.175							
W.R.	P_1 0.0363	0.0369	0.0292	27.5	2.05	1.62	1.77	7.6
	P_2 0.0375		0.0268	22.8	2.67	1.94		
	P_3 0.0369							

*P.
†U.
‡V.
§$C=\frac{UV}{P}$

Volumes of Distribution of Thiocyanate

Table 9 records the thiocyanate spaces as calculated from equation (4). They range from 30.17 to 38.09 per cent of body weight, with an average of 34.53 per cent. The relation of the volumes of distribution of thiocyanate to the amount of thiocyanate recovered in the dialysate is discussed below.

Discussion

The acceptance of any medicinal by the medical

profession depends on its therapeutic effectiveness and also on the frequency of severe side reactions. Sodium and potassium thiocyanate have been therapeutic successes in many cases of hypertension, but the high prevalence of untoward effects, occasionally resulting in death, has understandably dampened enthusiasm for this compound.

Once intoxication has occurred, the clinician has, in the past, been dependent solely on renal excretion of thiocyanate since a specific antidote has not been available. Renal excretion of this ion, however, is usually very slow and unpredictable. The renal clearance of thiocyanate in the human being as determined

TABLE 6. *Renal Clearance of Thiocyanate in Normal Subjects.*

SEX	AGE	UREA CLEARANCE	THIOCYANATE CLEARANCE	SERUM THIOCYANATE LEVEL	SOURCE
	yr.	*% of normal*	*cc./min.*	*mg./100 cc.*	
M	35	85	3.5	5.70	Wald et al.[6]
F	35	77	1.9	3.80	Wald et al.[6]
M	35	–	2.2	9.40	Moister & Freis[29]
M	36	–	1.5	9.33	Moister & Freis[5]
M	22	–	2.7	2.95	Present report
M	21	–	1.6	8.89	Present report
Average			2.2		

*Calculated from data published by authors.

from 6 normal controls averaged 2.2 cc. per minute (Table 6). Wald, Lindberg and Barker[6] reported an average renal clearance of 0.44 cc. per minute in 5 cases of either hypertension or chronic renal disease. The 2 patients with chronic renal disease described above had an average clearance of 1.26 cc. per minute (Table 5); in these cases thiocyanate clearances could not be correlated with urea clearances. A suggestion of this may be gleaned by inspection of Table

TABLE 7. *Dialysances* of Thiocyanate in 5 Patients with Chronic Renal Disease.*

PATIENT	DIALYSANCE OF THIOCYANATE
	cc./min.
F.R.	184.6
S.S.	211.9
F.W.	169.5
D.P.	168.3
W.R.	135.7
Average	174.0±27.8†

*Values determined from 1st 2 hr. of dialysis only; each patient value represents average of at least 4 determinations.
†Standard deviation.

5. Wald et al.[6] made similar observations in their patients.

It is apparent from these clearance values that most of the thiocyanate filtered at the glomerulus is reabsorbed by the tubule. However, very little is known about tubular reabsorption of thiocyanate.[23] Regardless of the exact renal mechanism involved, it is apparent that thiocyanate is excreted very slowly.*

By contrast, the dialysance of thiocyanate with the use of the artificial kidney is quite high: in patient S.S., for example, the average figure was 211.9 cc. per minute, whereas the renal clearance before dialysis was 0.76 cc. per minute; in patient W.R. the dialysance and clearance rates were 135.7 and 1.77 cc. per minute respectively. Thus, dialysis was 279 times more effective in clearing thiocyanate in patient S.S. and 77 times more effective in patient W.R. The average dialysance value of thiocyanate in 5 patients was 174.0 cc. per minute,† whereas the average clearance in 6 normal controls was 2.2 cc. per minute. Dialysis, then, is 79 times more effective on the average than the normal biologic kidneys in clearing thiocyanate.

TABLE 8. *Comparison of the Average Dialysance of Thiocyanate with that of Urea in 5 Patients with Chronic Renal Disease.*

BATH	DIALYSANCE OF THIOCYANATE	DIALYSANCE OF UREA
	cc./min.	*cc./min.*
1	174.0	200.6
2	178.5	222.7

From the data presented in Tables 3 and 4 it can be seen that the characteristics of dialysis are remarkably constant from patient to patient, regardless of the initial plasma thiocyanate level or of the total quantity of thiocyanate removed during dialysis. For example, of the total quantity of thiocyanate recovered during a six-hour dialysis, an average of 57.2 per cent (coefficient of variation, 12.6 per cent)‡ was removed during the first two hours in 6 individual runs, and 27.5 per cent (coefficient of variation, 12.4 per cent) was removed during the third and fourth hours. The plasma level was reduced an average of 58.8 per cent (coefficient of variation, 12.9 per cent)

TABLE 9. *Thiocyanate Spaces of 5 Patients Who Had Chronic Renal Disease without Edema.**

PATIENT	THIOCYANATE SPACE	PERCENTAGE BODY WEIGHT
	liters	
F.R.	23.23	34.41
S.S.	22.93	38.09
F.W.	20.69	33.58
D.P.	22.51	36.42
W.R.	20.03	30.17
Average		34.53±1.35†

*Calculated from average dialysance during 1st 2 hr. of dialysis and rate of decrease per unit of time of plasma-bath-concentration gradient using equation (4[1]).
†Standard deviation.

*The quantity of thiocyanate excreted in feces and perspiration is negligible.[5]
†Calculated from figures determined during the first two baths.
‡Calculated as $\frac{\text{standard error}}{\text{mean}} \times 100$.

during the first two hours of dialysis and 79.4 per cent (coefficient of variation, 8.3 per cent) after another two hours of dialysis. Since the reproducibility of these figures is quite good (as shown by the small coefficients of variation) it can reasonably be predicted in any given patient that the first two hours of thiocyanate dialysis are more effective than the last four. This might have been expected because the gradient between plasma and bath decreases steadily with time.

Thiocyanates have in the past been used to measure a space that approximates the extracellular fluids of the body.[12,24] The reported average values are approximately 20 to 23 per cent of the weight of normal subjects. The values obtained in our 5 patients (all of whom had terminal renal insufficiency without edema) by the method of calculation outlined above ranged from 30 to 38 per cent of body weight. These figures are almost identical with those reported by Lavietes, Bourdillon and Klinghoffer,[24] who determined the thiocyanate spaces by conventional technics in 4 patients with advanced renal insufficiency without edema; their values ranged from 30 to 43 per cent of body weight. Grollman and Shapiro[25] have also demonstrated increased extracellular fluid spaces in patients with hypertension who had no evidence of edema.

The quantity of thiocyanate recovered in the dialysate does not correlate exactly with the decrease in the plasma level of thiocyanate. An example of this is given in the section on results, where it is pointed out that patient L.D. had the greatest decrement in plasma thiocyanate level whereas her thiocyanate recovery in the dialysate was less than that of patient S.S. (Table 1). This is further illustrated in Table 1, where it is seen that F.R. had a drop in plasma thiocyanate level from 13.8 to 2.1 mg. per 100 cc. with a thiocyanate recovery of 2.96 gm., and patient F.W. sustained a more striking reduction in the plasma thiocyanate level, from 14.1 to 1.6 mg. per 100 cc. and yet the thiocyanate recovery was only 2.4 gm. This apparent discrepancy is explained when it is realized that F.W. had a thiocyanate space 2.54 liters smaller than that calculated for F.R. Because of the differences in the volumes of distribution of thiocyanate from patient to patient, it is seen that in general the initial plasma level is not an accurate guide to the subsequent amount of thiocyanate recovered in the dialysate.

It has been demonstrated that the majority of administered thiocyanate remains in the extracellular phase.[12,24] Although this undoubtedly contributes to the effectiveness of hemodialysis in cases of thiocyanate intoxication, it does not explain how the thiocyanate ion produces its toxic effects, especially its predilection for causing central-nervous-system symptoms. Tissue assays in cases of fatal thiocyanate poisoning have shown that the susceptibility of the central nervous system is not due to high concentrations of thiocyanate in the brain[9]; therefore, the mechanism whereby thiocyanate produces its toxic effects remains largely unknown.

Before 1950 the artificial kidney had been used chiefly in the removal of endogenous toxins or metabolites. Recent reports have demonstrated the effectiveness of hemodialysis in the removal of acetylsalicylic acid,[26] bromide[27] and barbiturates[28] from the body. Although sodium and potassium thiocyanate are not, at present, used as extensively in therapeutics as in the past, thiocyanates are still employed often enough to make the problem of thiocyanate poisoning of considerable clinical importance. This study demonstrates that thiocyanates can be removed much more efficiently by extracorporeal hemodialysis than by urinary excretion. It is suggested that hemodialysis on the artificial kidney is the most specific and effective therapy available at present for the treatment of thiocyanate intoxication.

Summary and Conclusions

Thiocyanates can be removed effectively from the human body by hemodialysis with the Kolff–Brigham artificial kidney.

The dialysance of thiocyanate in 5 patients was found to be 174.0 cc. per minute, comparing with an average of 2.2 cc. per minute for the renal clearance of thiocyanate in normal persons. Thus, hemodialysis is about 79 times more efficient than urinary excretion in clearing thiocyanate.

The dialysance of thiocyanate is of the same order of magnitude as that of urea, 174.0 and 200.6 cc. per minute, respectively.

Thiocyanate spaces were determined by means of the artificial kidney. These volumes of distribution were used to interpret the dynamics of thiocyanate dialysis.

Hemodialysis on the artificial kidney is recommended as the most effective and practical procedure in the treatment of thiocyanate intoxication.

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VARIATIONS IN THE VITAL-CAPACITY MEASUREMENT IN PATIENTS WITH BRONCHIAL ASTHMA AND PULMONARY EMPHYSEMA*

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ACCORDING to Myers[1] the earliest attempt to determine the inspiratory lung volume is attributed to Borelli, whose investigations were published in 1679. Subsequent investigators showed the vital capacity to be approximately 200 to 250 cubic inches.[2,3] Hutchinson[4] made a detailed study of the vital capacity of 3000 people and noted that it was influenced by such factors as age, disease, weight and height. Further studies confirmed these correlations, particularly that with surface area.[5,6] The influence of these factors is shown in various tables of normal vital-capacity measurements.[1] It is also well recognized that motivation, training and fatigue influence the accuracy of the method. The present study was conducted to ascertain the effect of the speed and force of expiration on the total volume of the vital capacity, with particular reference to patients with pulmonary disease.

Despite limitations, the measurement of vital capacity has long been used as a test of cardiorespiratory function. An increase in vital capacity occurring after inhalation of epinephrine in patients with bronchospasm was shown by Lageder.[7] In 1938 Barach[8] compared the vital capacity as recorded on a fast-moving drum before and after epinephrine and demonstrated not only an increase in the vital capacity but also an increased velocity of air movement during the respiratory cycle. During the performance of the determination of maximum breathing capacity patients with pulmonary emphysema trap air as a consequence of the incomplete emptying of the lungs.[9] Gaensler[10] stressed time as a factor and found a better correlation between ventilatory insufficiency and the volume of air expired per second on forced expiration ("timed" vital capacities) than when the total volume of the total capacity was used. In his procedure instructions to the patient call for as rapid an expiration as possible into the spirometer.

In the reports on vital capacity in the literature, instructions to the patients were not described in detail. In our experience variations in the results of serial determinations were traced in many cases to the speed or slowness with which this maneuver was executed. This study demonstrates the variations in the volume of expired gas resulting from changes in the rate (and force) of the expiratory effort.

METHODS

The vital capacity of normal subjects and patients with bronchial asthma and pulmonary emphysema was recorded as a graphic tracing by means of the Benedict–Roth spirometer and also on the McKesson–Scott spirometer. The subjects were first instructed to breathe slowly and steadily into the spirometer after a maximal inspiration. The best of three successive determinations was recorded and termed the "slow" vital capacity. After a rest period of five to ten minutes, a second test was carried out, with instructions to the patient to exhale as rapidly as possible into the apparatus. The best of three determinations was recorded as the "fast" vital capacity.

RESULTS

The results are recorded in Figure 1. The difference between the two measurements was calculated

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according to the following formula: slow minus fast vital capacity divided by fast vital capacity.

Control Groups

Slow and fast vital capacities were ascertained in 40 healthy control subjects. The average age of this group was forty-one years, with a range of twenty-nine to fifty-six years. The difference between the slow and fast capacity in 37 subjects (92 per cent of the group) was within the range of -5 to $+5$ per cent (Fig. 1). One patient was in the -5 to -10 per cent range, and 2 were in the $+5$ to $+20$ per cent range.

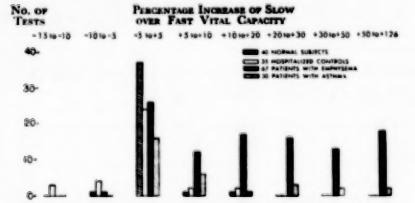

FIGURE 1. *Comparison of Fast and Slow Vital Capacity. The results are recorded in terms of the equation described in the text. The inequality between the two types of determination in patients with asthma or emphysema is apparent.*

Thirty-five hospitalized patients without cardiopulmonary disease were studied. The mean age of this group was fifty-six years (range, thirty-one to seventy-seven years). Twenty-four, or 69 per cent, fell in the -5 to $+5$ per cent range. Three patients were in the -10 to -15 per cent range, 4 in the -5 to -10 per cent range, and 2 each in the $+5$ to $+10$ per cent range and $+10$ to $+20$ per cent range.

Patients with Bronchial Asthma

Thirty patients were studied. The average age of this group was forty-eight years (range, thirty-four to sixty years). Anatomic chronic emphysema was excluded on the basis of history and physical findings. Bronchospasm was present in all cases at the time of the test. In this group 16 patients (53 per cent) were in the -5 to $+5$ per cent range. The remainder showed various degrees of difference in the two types of vital capacity, in some cases as high as 50 per cent (Fig. 1).

Patients with Pulmonary Emphysema

One hundred and three tests were performed in 67 patients with obstructive pulmonary emphysema with or without demonstrable bronchospasm. The average age was sixty years, with a range of twenty-seven to seventy-four years. In 26 (25 per cent of the total tests) the difference between the two tests was within the -5 to $+5$ per cent range. The remainder (75 per cent) showed a marked differential between the two capacity determinations, the highest being 126 per cent. Although these differences were not correlated with the degree of anatomic change in the lungs as seen on x-ray examination the largest percentage differences, so far as the clinical symptom of dyspnea was concerned, appeared to be in the patients with the most advanced emphysema.

Discussion

The results indicate that a considerable variation in the vital-capacity measurement is manifested in patients with bronchial asthma and a greater difference in those with pulmonary emphysema, depending on instructions regarding the performance of the test. A slight variation was observed in a few patients without these diseases. The marked decrease in the vital capacity that occurred when a rapid expiratory effort was attempted in bronchospastic disease is shown in Figure 2. In patients with pulmonary emphysema this response was characteristic of the majority of cases. The reason for the occasional case in which the slow vital capacity was smaller than the rapid was not apparent.

Retarded expiratory air flow, long recognized as a special disability in patients with pulmonary emphysema, has been the subject of pneumotachographic studies by Proctor, Hardy and McLean[11] and Dayman.[12] Collapse of the bronchi may occur on forced expiration or cough before maximal emptying of the lungs has been achieved as result of a relative increase of the intrapulmonary over the intrabronchial pressure.[12] A variable degree of functional emphysema is present in patients with bronchial asthma during episodes of persistent bronchospasm. Expiration is then handicapped by the same check-valve mecha-

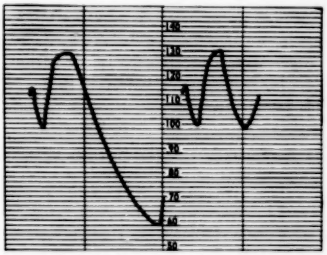

FIGURE 2. *Graphic Tracing of the Unequal Vital-Capacity Volumes on a Sixty-Four-Year-Old Man with Advanced Pulmonary Emphysema.*

The tracing was made on a Benedict–Roth spirometer and recorded on a rapidly moving drum. The record is read from left to right. The ascending slope represents inspiration, and the descending slope expiration — in this case the vital capacity.

nism as occurs in anatomic emphysema. The value of pursed-lip breathing in the treatment of patients with pulmonary emphysema has been associated with the slow expiration produced in this type of respiration, as well as the tendency of back pressure to keep the bronchi patent. From a therapeutic point of view, a lesson is confirmed by the findings of this study — namely, that a better emptying of the lungs is obtained by a slow expiration in the presence of bronchial obstruction. To meet the ventilatory needs of such persons, a rapid inspiration and a prolonged expiration may be justified. The need for careful instructions in the performance of the vital-capacity test in patients with asthma and emphysema appears quite clear. It is suggested that a slow expiration more nearly meets the definition of the test when used for the maximal amount of air a patient may expel from the lungs after a deep inspiration.

Summary

The effect of the rate of expiration on the measurement of vital capacity was studied in a group of 75 control subjects and 97 patients with bronchial asthma and pulmonary emphysema. The results were classified as slow minus fast vital capacity divided by fast vital capacity. In the control group 37 of 40 healthy subjects showed a deviation of less than −5 to +5 per cent between the two capacity determinations. Of 35 hospitalized patients without cardiopulmonary disease, 24 were within this range, with a slight scatter in the other 11 patients.

In 14 of 30 patients with bronchial asthma the differential increase in the slow capacity over the rapid was between 5 and up to 50 per cent.

In 103 determinations in 67 patients with obstructive pulmonary emphysema only 26 tests fell in the −5 to +5 per cent range; in the remainder (75 per cent of the tests) showing differences between the two types of capacity, determinations were between 5 and 126 per cent. In half these cases the variation was considerable — that is, 30 to 126 per cent.

The cause of this variation is discussed, and the necessity for uniform performance of the vital-capacity determination is emphasized.

The observed differences between the slow and fast vital-capacity determinations encountered in this series did not appear to be influenced by the order in which the determinations were performed. In an additional 30 patients with pulmonary emphysema the fast vital-capacity test was performed before the slow test. The slow vital capacity exceeded the fast by 40 per cent or more in 8 of the 30 patients, and by more than 50 per cent in 5.

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MEDICAL PROGRESS

ELECTROENCEPHALOGRAPHY (Concluded)

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BOSTON

The successive anatomic structures (1, 2, 3 and 4 below) traversed or penetrated by the impulses of the neurons that constitute the nonspecific afferent system are as follows:

(1) Reticular formation and periaqueductal gray matter of brain stem.
(2) Subthalamus and hypothalamus adjacent to third ventricle.
(3) Thalamus.
(4) Cerebral cortex.

There is also (3′) a parallel extrathalamic avenue describable as follows:

(2) Subthalamus and hypothalamus adjacent to third ventricle.
(3′) Internal capsule.
(4) Cerebral cortex.

The course that these impulses take through (3) the thalamus and thence into (4) the cerebral cortex is especially controversial, and its description may be ventured as follows:

(2) Subthalamus and hypothalamus adjacent to third ventricle.
(3*A*) Centrum medianum, nucleus centralis, and nucleus centralis lateralis, all 3 of which are called by some anatomists intralaminar nuclei of the thalamus.

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(3*B*) The association nuclei of the thalamus as listed below.
(4) Different parts of the cerebral cortex as listed below.

(The impulses travel — that is, from 2 through 3*A* and thence through 3*B* and thence into 4.)

The (3*B*) association nuclei of the thalamus and (4) the different parts of the cortex into which they send impulses may be ventured as follows: (j) dorsomedial nucleus, to prefrontal (granular) cortex; (ij) nucleus lateralis dorsalis, to parietal cortex; (ij) nucleus lateralis posterior, also to the parietal cortex; and (iv) pulvinar, to parietotemporal and parietooccipital cortex. There is evidence that such impulses reach primary receptive areas of the cortex[50] and the cortex of the temporal lobe[51] as well as the parts of the cortex just listed.

Cobb[52] integrates the scheme given above with earlier work of Ranson and with work of Hess by the following elaboration:

> . . . stimuli from the environment (i.e., from the outside world) travel by afferent tracts to the reticular formation of the brain stem and to subthalamus, hypothalamus and thalamus; a "wakefulness center" in the hypothalamus plays on the thalamus and keeps it active . . . Injuries to the hypothalamic area could interrupt Ranson's tract which keeps the thalamus awake. Stimulation of the massa intermedia of the thalamus can inhibit this and cause sleep [as described by Hess].

An important recent review of thalamic connections is that of Droogleever Fortuyn.[53]

From the cortex of his *cerveau isolé*, which was severed from the greater part of its brain-stem reticular formation and periaqueductal gray matter, Bremer recorded high-voltage slow waves like those of sleep.[18] Moruzzi and Magoun stimulated by electric shocks the brain-stem reticular formation of their *encéphale isolé*, and, in the electric record from its cortex, they saw the brain waves change from high-voltage slow oscillations like those of sleep to low-voltage fast oscillations like those of the waking state.[24] Jasper, by electric shocks to the mesial thalamus, produced wave-spike activity like that of epilepsy in the cortex of the stimulated brain[25] (and at the same time behavior like that of a patient with an epileptic seizure). Dempsey and Morison, by regular electric stimulation of the dorsomedial region of the thalamus, caused potential oscillations of the same frequency in the cerebral cortex.[27-29] All these effects were mentioned in the discussion of rhythmicity. The nonspecific afferent system is adequate to mediate them all. Because of its relation to wakefulness and sleep, it is also often called "the reticular activating system." In elaboration of this aspect of the system, French and his associates have said,[48] "excitation of this area [brain stem reticular formation and periaqueductal gray matter] by repetitive stimuli delivered directly to it or to peripheral sensory receptors results in electrocortical desynchronization [a change from high-voltage slow to low-voltage fast waves] and behavioral arousal of a sleeping animal." In short, activity of the nonspecific afferent system is apparently specific for that common aspect of all sensations, consciousness in the waking state.

Activation

The electroencephalogram can be influenced by a number of things that can be controlled. Such influences have clinical diagnostic value, and the word "activation" generally designates their use in this way. In general their diagnostic application depends on the demonstration of a focal or asymmetrical response or diffuse and unusually sensitive response to the influence. A few of the methods of activation currently in widest use are considered here.

Metrazol given intravenously has long been in vogue as a means of activation. It may elicit symmetrical, diffusely asymmetrical or focal responses. It is said to elicit different kinds of waves corresponding to different kinds of seizures. (In my limited experience the different kinds of waves look as alike as peas.) Its commonest use has been to establish thresholds of response, with the idea that a patient with epilepsy will respond to a smaller dose than one without epilepsy. Individual laboratories may have had their own control series and standards for administration, but for a long time none were reported. The deficiency has finally been corrected by the studies of Fuglsang-Frederiksen[54] and Buchthal and Lennox.[55] They give admirable and surely adequate data for young men in and around the third decade. The strict limitation of age and sex should be borne in mind when their standards are applied to other ages and sexes.

Photic stimulation (flashing a light in the subject's eyes, usually at regular intervals, including notably a frequency of 15 flashes per second), combined with opening and closing the eyes, elicits a spectrum of reactions ranging from no visible change under ordinary recording conditions, through occipital brain waves at the same frequencies as the flashes, to diffuse high-voltage paroxysmal waves, which, in extreme cases, persist after the flashes stop and go on to become the dysrhythmic activity attending an epileptic seizure. The last occurrence is rare. Usually, the paroxysmal response is brief and stops even while the flashes continue. Paroxysmal responses are easily distinguished from nonparoxysmal and are regularly associated with other evidence of epilepsy.

One-sided posterior cerebral abnormality is sometimes but not always attended by a nonparoxysmal photic driving response that is of higher voltage on one side than on the other. Curiously enough, the higher voltages apparently occur quite regularly on the same side as the abnormality. This effect has been reported by Weil,[56] who has observed it from time to time in the course of routine clinical interpretations. Its study is a proper object of research. Photic stimulation is part of the routine clinical elec-

troencephalographic investigation in many laboratories. A review by Brazier[57] of its physiologic significance has recently been published.

Activation by the combined use of photic stimulation and Metrazol has awakened great interest. As far as I have been able to discover, it was first reported by Rémond and Gastaut,[58] who provided at least one unequivocal example of an asymmetrical response. As yet, the test has not proved successful as a means of establishing thresholds of response that are of diagnostic value. Indeed, the thresholds for different groups of subjects have been so various that one critic facetiously suggested that one might predicate a special threshold for menstruating Negro women bus drivers from Texas.[59] Such levity should not, however, distract one from the challenging physiologic significance and diagnostic potentialities of the procedure.

It is apparently a matter of universal agreement that sleep is of supreme value in eliciting the spiking that attends psychomotor epilepsy and is usually recorded from the temporal lobes. This is true for sleep occurring naturally or in response to drugs. The value of sleep in activating other types of dysrhythmic patterns that attend the epilepsies is more controversial.

When the sleeping patient is disturbed characteristic slow waves occur.[7] Grossman[60,61] has shown that, in patients who have unilateral brain lesions, these waves are suppressed on the side of the lesion. It is evident that activation offers to the clinical electroencephalographer stimulating possibilities for dynamic understanding that are yet to be explored.

The whole subject of activation has been dealt with in a recently published symposium held in August, 1953.[62]

Epilepsy

Epilepsy has been from the first and continues to be a favorite concern of electroencephalographers. In 1937 the Gibbses and Lennox[63] declared that epilepsy was a cerebral dysrhythmia. Jasper and Nichols[64] made a similar early pronouncement and went on to observe that "brain mechanisms in epilepsy are . . . seen to be merely extreme variations of the mechanisms of normal brain function." In the ensuing years these early views have been confirmed and elaborated. Epilepsy can be regarded as a running amuck of the normal electric rhythmicity of neuronal aggregates that has already been discussed. In what follows each among several aspects of the epilepsies is considered as the abnormal counterpart to some aspect of the normal rhythmicity.

The liability of epileptic patients to seizures varies widely, being comparable to the wide range in the amounts and kinds of rhythms shown by normal subjects. Kershman and Hunter[65-67] have made an especially fine study, including an admirable follow-up report, of subjects with rare seizures and normal or mildly abnormal electroencephalograms. Their study, which establishes the very good prognosis in such cases, has been confirmed by other work. Only their espousal of the euphemism "encephalosyncope" may err on the side of semantic gymnastics.

Epileptic patients, like normal subjects, show a wide range of response to different kinds of activation, particularly to photic stimulation and to intravenous administration of Metrazol.

As a group they show stronger electrocortical responses to photic stimulation than nonepileptic persons do and probably alone show paroxysmal responses. It is now well established that a few very responsive patients are subject to short lapses precipitated by flickering light.[69-71] Before the advent of electroencephalography, Gowers,[72] for one, had reported seizures precipitated by changing light. Adrian pointed the way to electroencephalographers. Walter[73] made extensive studies of the electroencephalographic responses of epileptic patients stimulated photically but never chanced to induce a seizure in any of his subjects. It remained for Cobb[74] to bring photogenic epilepsy into direct relation with current electroencephalographic work on the photic "driving" of brain waves. While reading a paper that Earl Walker had written on the subject, he recalled from among his epileptic patients 1 who had attributed his seizures to the effect of flickering light. By a further effort of memory he recalled from his practice 2 similar cases. For these 3 patients he postulated an extreme response that culminated in clinical seizures and was the pathologic extension of the response described in Walker's paper. The histories of these patients and reference to the stimulating article by Walker are recorded in the short paper that Cobb[74] then presented. His theory regarding these 3 patients was soon confirmed experimentally in other cases. A number of such cases have been reported, and a larger number have been observed.[69-71]

Children who are liable to such seizures may induce them deliberately by waving their hands back and forth before their eyes.[75] This activity may be like that of the normal child who takes pleasure in spinning around and around until he has induced a transient labyrinthian vertigo. Perhaps for the epileptic child some surcease of consciousness is an added premium. From a practical point of view, it appears that for some of these patients green spectacles[70,71,76] afford protection against this untoward epileptogenic effect of flickering light.

The studies by Fuglsang-Frederiksen[54] and Buchthal and Lennox,[55] which have already been mentioned, show that epileptic and nonepileptic persons alike display wide and overlapping ranges of response to intravenous administration of Metrazol. In more detail, Metrazol is given intravenously in amounts of 100 mg. per kilogram of body weight and thereafter 50 mg. every thirty seconds to not more than 350 mg. Among definitely nonepileptic subjects a few respond to this dosage by showing paroxysmal

activity with or without seizures, but most are resistant; among subjects suspected of epilepsy, a larger number respond in this way, and fewer are resistant; and among those having clinically established epilepsy the largest number of subjects respond in this way, and the smallest are resistant.

Experience accords well with two unifying assumptions. One of these is that the clinical and electric manifestations of a seizure are both determined by the aggregate or aggregates of neurons where abnormal rhythmic — that is, dysrhythmic — activity occurs. The other is that the abnormal activity may begin in one aggregate and then, by axonal impulses or even neighborhood electric effects, may stimulate dysrhythmic activity in one or more other aggregates. (In passing it may be noted that the dysrhythmia can begin and can even throughout the whole course of a seizure persist in an aggregate so remote from the electrodes that one happens to be using that it cannot be recorded and only normal-appearing activity appears in the electroencephalogram.) Both these assumptions entail analogies between normal processes and epileptic processes that are derivations of the normal ones.

One of these is that the protean variety of clinical disturbances that constitute epileptic seizures corresponds well with the multiplicity of neuronal aggregates, each of which has its own normal rhythmicity and mediates one or more normal processes and each of which is subject to a dysrhythmia with corresponding clinical disturbances of the normal processes. One could perhaps say truthfully that the manifestations of epilepsy are as protean as the processes mediated by the central nervous system, — the less familiar modifications of appetite or thirst, goose flesh, chilly or feverish feelings, and peculiarities of thinking and behaving, in addition to the classic auras, other sensations, alterations of consciousness with or without its obliteration, motor activity, urination and defecation, — each determined by dysrhythmia in the one or more aggregates most essential to its normal counterpart. Penfield and Kristiansen[77] have dealt in detail with the practical value of such observations for diagnostic localization.

A few such effects may be considered at greater length. Thus, I recently saw a patient whose diffuse, symmetrical paresthesias were very like the effects that Penfield[25] elicited by stimulation of the secondary sensory area.

Janjigian[78] has reported the case of a patient whose electroencephalogram compelled respect for the unexpected diagnosis of cardiac epilepsy as the explanation for his attacks of angina pectoris. Dilantin proved therapeutically effective. Similar but unpublished and less adequately studied cases have come to his attention.[79]

The syndrome of abdominal epilepsy,[80-93] which could hardly have been recognized without the electroencephalogram, appears to be well established and of fairly frequent occurrence, though I have never seen a well attested case and, puzzlingly enough, find the same lack of experience among most of my colleagues. The references given here constitute a comprehensive bibliography, which is not readily found elsewhere. Though not the first to write on the subject, Moore,[88-89] referring often to the same cases, has covered the subject more extensively than others, who, however, have reported larger series of cases. Moore properly stresses the occasional occurrence of the condition in adults. Others give a more unified picture of a disorder of childhood and, to a lesser extent, of the first three decades. The literature contains 2 cases of peculiar interest. One[93] is the account of a ten-year-old boy who had an attack of abdominal epilepsy during the recording of his electroencephalogram. He reported the onset of his abdominal pain at a time when the tracing was relatively normal, but about two seconds later it filled with high-voltage paroxysmal activity; a reproduction of the electroencephalogram is completely convincing. The other case[81] is that of a fifteen-year-old girl who had an attack while gastrointestinal x-ray studies were being carried out; the x-ray film showed an intussusception of the terminal ileum. Intussusception had been postulated in the earliest reports[94] as a cause for the acute pain that characterizes the syndrome. Therapeutically, Dilantin has been so effective that its administration may constitute a diagnostic test.

Regarding psychomotor epilepsy space suffices only for the mention of a few considerations and one fact that is relevant to the general thesis that epileptic disturbances can be viewed as abnormal variants of normal processes. This fact, a matter of common experience and agreement, is that the spiking diagnostically typical of psychomotor epilepsy is recorded less often from structurally abnormal tissue than from tissue that is structurally normal and, furthermore, remote from the probable epileptogenic lesion when such a lesion can be demonstrated. This is the central consideration in a mass of evidence that the abnormal activity typical of psychomotor epilepsy arises in the tissue from which it is recorded as a result of abnormal impulses transmitted to that tissue from other parts of the brain. This is therefore an abnormal variant of the normal intercommunication between different parts of the central nervous system. Penfield and Baldwin[95] stress incisural sclerosis as a lesion causing psychomotor epilepsy. Recent papers by Gastaut and his associates[96,97] are of great importance for experimental and theoretical elaboration of this subject. Among other items, they include statistics showing the occurrence of such spiking in structures other than the temporal lobes. These figures correct the common overemphasis on the temporal-lobe distribution of such spiking. Between seizures the spikes are random, irregularly timed events. This is a contrast to the rhythmicity that has been emphasized so much and a salutary correction to that emphasis. The rhythmical regularity of the spikes during seizures may result from an acceleration of random occur-

rences to a frequency at which the constant refractory period of the affected neurons imposes regular intervals between occurrences. Some similar process may play a part in other instances of rhythmicity, normal and abnormal. The important and almost universally neglected paper by Fuster, Gibbs and Gibbs[98] is called to the attention of the historically minded reader who would trace the history of the distinguished contributions that the Gibbses and their collaborators have made to this subject. In this paper[98] the confusion between diffuse positive spikes and focal temporal negative spikes is first and finally elucidated.

There has been a continual interplay between physiologic investigation and the study of epilepsy. The former, stressed here, has been concerned with neuronal interconnections between the cortex on the one hand and, on the other hand, centrally located structures, including notably the thalamus and brain-stem reticular formation. Leaders in the study of epilepsy have been similarly oriented, as perhaps best reflected in two recent books. One of these is the comprehensive, massive and detailed volume by Penfield and Jasper.[25] The other is the comprehensive, slender and incisive volume by Gastaut.[99] It is probably correct to say that the central theme of the volume by Penfield and Jasper is the role assigned to what they designate as "the centrencephalic system." This they define grossly as "the neurone systems which are symmetrically connected with both cerebral hemispheres and which serve to coordinate their function." Elaborating and refining their definition, they say that these circuits are located in the brain stem, and they quote Herrick in defining the brain stem as "all of the brain except the cerebellum and cerebral cortex and their dependencies." They state explicitly that this includes thalamus, diencephalon, mesencephalon and rhomboencephalon. They do not specify what structures are excepted as dependencies of cerebellum and cerebral cortex. Presumably, they have in mind such large efferent structures as the pyramidal tracts or afferent connections that bypass synaptic connections in the centrencephalic system. They acknowledge the adventurousness of their point of view by granting that "a great deal of critical study must be carried out before the centrencephalic system is converted from hypothetical structure into proved anatomical system." Their masterful volume is designed to show what strong "support the study of epilepsy and neurophysiological observations . . . brings to this concept."

Gastaut, in the opening pages of his book,[99] offers a similar orientation. ". . . the custom of dividing the brain into two systems (cortical areas and subcortical nuclei, separated by a thick layer of white matter) has given way," he says, "to a differentiation into sectors defined by thalamo-cortical systems. . . . " He then distinguishes between the "partial epilepsies," which "are developed in a sector of a single hemisphere," and "the generalized epilepsies," which are apparently initiated in structures that would be included in the centrencephalic system of Penfield and Jasper. The "partial epilepsies" include, for instance, gustatory and visual seizures, jacksonian seizures and *epilepsia partialis*. The "generalized epilepsies" include notably grand-mal and petit-mal seizures.

The early distinction between fast-wave, slow-wave and mixed-fast-and-slow epilepsies that was ventured by Lennox and the Gibbses seems at present to be giving place to the point of view reflected here whereas others of their classic contributions stand with unimpaired importance.

Diagnostic Electroencephalography

The different kinds of electroencephalograms that have been recorded from patients with various diseases are well reviewed by Schwab.[100] Other reviews are provided by Strauss, Ostow and Greenstein[101] through 1947, by the Gibbs's *Atlas*[102] and by Cohn's atlas.[103] Comprehensive annual reviews by Brazier[104] cover the ground for the most recent years.

Recent advances in electroencephalography, as they have been presented here, are largely observations about a system of neurons occupying and extending from the reticular formation of the brain stem around and through the thalamus to the cerebral cortex, which it penetrates. The system as a whole or perhaps one or another selection of its neurons is called variously "the nonspecific afferent system," "the reticular activating system" and "the centrencephalic system." It is woven through and perhaps sometimes constitutes the bulk of many gross anatomic structures, most of which were listed tentatively in the description of the course of the nonspecific afferent system, but the system is by no means identical with all the gross anatomic structures through which it is interwoven. Thus, it may constitute the bulk of the brain-stem reticular formation; it can hardly be supposed, however, to constitute the bulk of the cerebral cortex, into which it penetrates. Apparently, it is a functional and largely microscopic not a gross anatomic unit. Its anatomic location is adapted to its mediation of impulses that will affect the activity, reflected in the electroencephalogram, of the cerebral cortex diffusely and symmetrically. Variations of the activity of this nonspecific afferent system are supposed to be the one factor common to three notably distinct classes of events that are observed experimentally to have a close association with each other and are variations in states of consciousness, variations diffuse and symmetrical of electrocortical activity and epileptic seizures that are not restricted to focal cortical manifestations. Delimitation of the system implies a distinction between the system, by whatever of its names it may be called, on the one hand, and, on the other hand, what may be called the cerebral cortical system.[31] This point of view has modified the clinical attitude toward epilepsy. To recapitulate that attitude by a concise example: in

a jacksonian seizure the events are of a focal cortical nature up to the point where the dysrhythmia extends to the centrencephalic system and, simultaneously, consciousness is lost.

This advance in electroencephalography has also been reflected in a number of clinical papers[105-107] about variations in consciousness that attend brain-stem lesions, traumatic, vascular or neoplastic. Finally, the psychiatrist may be interested by the similarity that the anatomic distinction between centrencephalic and cerebrocortical systems bears to the introspective distinction between oneself as observer and all sorts of subjective observations (dreams, hallucinations and the sensations of a jacksonian seizure before consciousness is lost, for instance).

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MEDICAL INTELLIGENCE

CONVERSATIONS WITH FRIEDRICH von MÜLLER

THE death of Friedrich von Müller, of Munich, in 1941, during the troublesome years of World War II, passed almost unnoticed in the British and American medical literature of that day. An obituary notice in the *Schweizer medizinische Wochenschrift* for November 29, however, caught the eye of J. D. Rolleston, who wrote an appreciative note in *Nature* for February 14, 1942, recalling Müller's early papers on metabolism, his famous description of 2 fasting men (1893) and commenting on his clinic, one of the most largely attended in Europe, where many British and American students went for courses in postgraduate education. The story of that clinic must be told elsewhere, but in passing one notes the large number of Canadian and American students who attended. When Osler went to Munich for the Congress of Internal Medicine in April, 1906, he found Campbell Howard hard at work, and Osler spent most of his time with Müller, establishing a friendship that lasted until Osler's death in 1919, despite the feeling in Oxford engendered by World War I. Revere, Osler's son, carried in his war kit a letter to Müller to be used in case of capture.

After Osler a long list of British, Canadian and American students went to Müller: Canby Robinson, George Draper, Karl Vogel, Lindsay Williams, Henry James, Eugene Du Bois, Rollin Woodyatt, George Fahr, Ralph Major, Cecil Watson, William McCann, David Barr, Warren Sisson, Arthur Hurst and many others; Siegfried Thannhauser, now in America, was his chief-of-staff for many years. Garrison thought Müller the most scientific teacher of internal medicine of his day, and Abraham Flexner, in 1912, after visiting the clinic, wrote, "A master mind at work is exhibited daily to two hundred students or more." Sisson, when only a second-year medical student, found him "one of the most dynamic, forceful and exact teachers I ever had and although austere, . . . fundamentally most friendly," and Robinson recalls his critical judgment, clear, forcible and appropriate expression, as well as his personal magnetism, sense of humor and sympathy, in an article written soon after his return to America for the *Old Dominion Journal of Medicine and Surgery* (1909).

Ten years after Müller's death, H. W. Siemens, his son-in-law and professor of dermatology in Leiden, wrote a tribute in the *Münchener medizinische Wochenschrift*. Siemens had spent the last summer of Müller's life in 1941 with him in Munich and fortunately jotted down some characteristic remarks of this exemplary teacher that serve to bring back to his students a vivid picture of Bavarian humor, warmth of personality and broad cultural outlook. Excerpts from these notes, translated from the German by

Friedrich von Müller (Reproduced by Permission of Münchener medizinische Wochenschrift).

Fredrick Gudernatsch, are published with the permission of the *Münchener medizinische Wochenschrift*.

What I fear most in science is dogma. Orthodoxy is the root of all evil. (From an after-dinner speech on his eightieth birthday.)

I care nothing for what is called "Standpunkt" (standpoint-conviction). When a man sticks to his fixed notions, things are warped right from the start. It is always a mistake to cling to preconceived ideas.

The ideal every hospital administrator has in mind is a hospital without sick people.

He who has made mistakes himself and is aware of them, can offer the most useful criticism.

Wotan as a God is nothing but a myth. The old Germanic people had no religion whatever, but they had wise women and the like. "Magic" will always be needed, even in medicine. Just now I am taking care of a typhoid patient. When she gets well, everybody will say "it was Müller who cured her."

When I was a boy, a "magician" used to come to our fairs. He *really* could do "magic" things. I *actually* saw him do them.

The "ladder system" under which he who is on the lowest rung can figure out how long it will take him to get to the top, spells the death knell for any Faculty.

In an after-dinner speech during his stay in America,

Friedrich von Müller compared the hardships of an academic career with the strenuous efforts made by Bavarian youths at harvest celebrations when they try to climb a greased metal pole so as to catch the prize sausage hung from the top. "If they wish many men to go to such trouble, they had better hang a pretty big sausage on the pole," he said. From then on, his American colleagues called him "the man with the big sausage."

I wish I were a policeman. It must be wonderful always to have the power to forbid something — and always something that isn't of much importance anyhow.

In the history of the human race, danger to established order and upheaval never were brought on by elementary causes, as starvation for example, but always by powerful ideas: Alexander the Great; Luther; French Revolution.

When I see the Venus de Milo, I always think: I should like to be invited to tea by her. She is a highly cultured lady and it must be a pleasure to chat with her.

Revengefulness will never be a sound motive for action.

The Parthenon frieze in London is to me the acme of Greek art. What majestic peacefulness and what magnificent flow of garments! — On the other hand, the Pergamum relief in Berlin seems to me a bit too baroque.

If you do not appreciate Raphael, there is one remedy: just try and copy him.

I do not care much for Schubert's "Unfinished Symphony" because it has too many repetitions. The composer put too few thoughts into it. Neither do I like Beethoven's "Ninth" so very much, especially its last two movements.

Answering the question as to what Krehl might be talking about in his next address: "Oh, about religion and medicine as usual."

It is one of the greatest problems of faith: why does evil triumph so often?

Even the dullest man has something that interests him. To lead him on to that, therein lies the art of conversation.

Plutocracy in itself is evil; but — he who pays the bill also must have the right to sound his voice. — My ideal is the set-up in Washington with the provision for a presidential term of four years. It is a masterpiece. Yet, judging from the memoirs of Carl Schurz, it did not fully stand the test, because power rests with the voters, not with the government. — The monarchical system is unsound. One of its weaknesses is that it leaves to the Almighty what should be regulated by the people themselves.

Changes in our election laws should begin by raising the voting age and withholding the voting right from women. As a rule, women are apt to fall for the "latest trends" still more readily than men.

What is of importance in clinical medicine is insight and understanding, not just book-learning. I never read a textbook of internal medicine completely through; I always got stuck in it somewhere.

Concerning naturopathy, cold water cures and the like: these "cults," too, will vanish in time as others have. — Homeopathy operates under wrong concepts: "that one must fight disease with its own causes (similia similibus), and that medicinal agents have their greatest effect when given in highest dilutions." — Far, far from such a path we must follow our own, always trying to be as exact as possible, as reliable as possible.

In medical practice it often amounts to this: the remedy a patient takes just before getting well is the one to which goes all the credit.

Every chief must learn to allow his assistants to work out not only his ideas but also their own.

An assistant who cares for his chief does not hesitate to stand up against him.

Beside his general medical training, a clinical assistant should also be well versed in a special discipline: chemistry, physics, physiology, or some other. The relationship between chief and assistant should be like that prevailing in a well founded marriage: both partners must bring something worthwhile into the union.

Students will always be duped by a professor as long as he is a glib orator.

Giving brush-up (post-graduate) courses may not always turn out to your advantage. If you do not give them, somebody else will, and you won't like that. If you do, the practitioners will no longer find it necessary to come to you for consultation. In former days some Nuremberg doctors would regularly call me in for consultation. After I had consented to give them a series of extension courses, nobody ever called me again. Those doctors were saying: "We already know what Müller would advise us to do."

In England a disciple feels in honor bound to call his former chief in for consultations — "so as to let him, too, earn a pound." In Germany, on the other hand, it has become the custom for former students and collaborators to push him from whom they got all their experience aside as far as possible. How does the Bible put it: "they had great esteem for him, they listened to him, but they never consulted him."

The first step to be taken in any new line of research is testing the methods which are to be used.

When it comes to the chemistry of metabolism, I am a purely self-taught man. Rubner and Voit would always quote from their own researches only. It wasn't until I began reading the literature that I came to realize that there existed still another "chemistry of metabolism," that of Hoppe-Seyler. The thorough study of Maly's "Physiologisch-Chemische Jahresberichte" helped me along more than anything else.

1934. Speaking of the political strife in Germany: these feuds originated from "religious" quarrels, they all are matters of "faith," as were those between the Protestants and the Catholics at the time of the Thirty Years' War. "*This* is the truth" some would say, and "*that* is the truth" say the others. "*Ours* is God's truth — and he who doesn't believe it, will be shot!" There is little sense in discussing these things. — Many think that soon a crash will do away with it all. That is just wishful thinking; for, there still are too many of the "Faithful."

In the present political set-up the basic question for everyone of us is this: shall he take his seat by the side of the chauffeur and try to influence the course — or shall he run behind the car and shout "Stop"? I am for the latter in order to gain time. If you sit with the driver, he is not going to let you handle the steering wheel, anyhow, and if someone smashes the windshield, you too will get hit.

Political convictions can best be appreciated when you take them as manifestations of some of the most primitive instincts of man; for instance, wanting to force oneself into a position held by someone else.

Concerning the legality of forced expropriations: "All those who have no property find the procedure strictly rightful."

1935. The only definite thing we know concerning Germany is that they are going to take our money away from us somehow. It is just the method as to which they do not agree as yet.

1937. I cannot live just from paying taxes.

The world wants to be left in peace, the politicians want extremes.

When I enter the hospital they all "Heil" me. I have my briefcase in one hand, my cane in the other, and a cigar in my mouth. Thus, how could I say, "Heil Hitler"?

During the past few years I made it a point to be very frank about everything. When the crown prince came in to see me, I always spoke of it openly so that people would remark: "Müller himself told me so." — When I gave help to a Jewish friend, for instance to my colleague L., I talked about it everywhere telling that Mrs. L. was over to dinner the other day. Don't be secretive about anything! Keep your visor open! That is your best protection.

1938. The present times are terrible. They remind me too much of the tension prevailing during the summer of 1914.

It has become impossible for us to imagine that there ever was an era as unpolitical as the one in which we grew up.

1939. People lose their incentive to work when the government becomes the enemy of the citizens and exploits them. Generally speaking, a man will be willing to

work from morning till night only when he can work for his home and family.

In recent years, Krehl, Minkowsky and myself came to be looked upon as the guardians of German medicine. The most outstanding, by far, was Minkowsky. Yet, he had some difficulties to overcome since he was Jewish. I made every effort, with the help of Leichtenstern, to get him a teaching position at the University of Cologne. At last I succeeded. Minkowsky never forgot and remained extremely grateful to me for the rest of his life.

It would not profit us to regain Alsace. The Alsatians cuss the French and also cuss the Germans. The German group at the magnificent Strassbourg University remained totally isolated from the rest of the population. Charlemagne had the right idea when he set up Alsace as a buffer state.

A real unification of North and South Germany could come about only if they establish separate government departments for education and religion. Bavaria cannot be governed from Hamburg, nor Austria from Berlin. The differences are too great. Each part has to get home rule such as the English gave to Ireland. — The same would apply to Czechoslovakia.

Concerning the old League of Nations: all that is left of it are a few secretaries wringing their hands and searching for a guiding principle.

CASE RECORDS
OF THE
MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

BENJAMIN CASTLEMAN, M.D., *Editor*

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CASE 41021

PRESENTATION OF CASE

A forty-six-year-old Estonian, mother of four, was admitted to the hospital because of pain in the right side of the abdomen.

The history was elicited with difficulty because of a language handicap. The patient had always thought herself in good health until a year before admission, when she noted that "sweets," "spices" and fried food caused a burning epigastric pain, so that she had limited her diet during the past year to soups, fish and vegetables and had avoided meats. The epigastric pain occasionally radiated to the back and to both lower quadrants, and was related in an unclear fashion to a different type of pain in the right upper quadrant that was not as distinctly related to diet, was occasionally produced by excitement and sometimes awakened her at night. The epigastric pain on occasion was associated with vomiting of a scant amount of nonsour white material, which tended to relieve the pain. The pain was not relieved by milk or antacids; it had been occurring once or twice monthly for the past year, gradually becoming more severe, and then gradually disappeared over a period of four or five days. Occasionally, it was so severe as to cause her to "double up," and it was sufficiently disabling so that she had not felt inclined to seek employment during the past year. Two months before admission she noted occasional black, loose stools. Six weeks later epigastric burning, gnawing pain, anorexia, vomiting and right-sided abdominal pain recurred. She ate very little during the ensuing week. Two days before admission she vomited a finger-sized blood clot. She continued vomiting the next day and consulted her family physician, who referred her to the hospital.

She had never been jaundiced, and denied light stools or dark urine, chills or fever. She described herself as always a "nervous person and a worrier"; this condition was made worse by her being taken from her native land to Germany and by her husband's deportation to Siberia. Her eight years in Germany were those of food deprivation. There had been a reduction in weight over the past year from 205 to 122 pounds. However, her average weight for years had been about 120 pounds, and the rise to 205 had coincided with temporary employment as a kitchen helper, where she had eaten "all the time." Fourteen months previously she had been admitted to another hospital, where gall-bladder study showed good dye concentration, slight delay in emptying and no stones; a gastrointestinal series was negative.

Physical examination revealed a chronically ill woman with a dry, pale skin who appeared older than her stated age. The tongue was red and furrowed with ulcers at the tip. Except for a Grade 1, soft, apical systolic murmur examination of the heart was negative. The lungs were clear. The liver was slightly enlarged; its edge was smooth and tender. Some observers reported the splenic tip barely palpable, and others could not feel the spleen. There was a sensation of fullness in the right lower quadrant and around the umbilicus and slight tenderness just to the right of the umbilicus.

The temperature was 99°F., the pulse 90, and the respirations 18. The blood pressure was 140 systolic, 68 diastolic.

Examination of the urine was negative; the urinary urobilinogen was 0.35 Ehrlich units. Examination of the blood showed a hemoglobin of 12.5 gm. per 100 cc. and a white-cell count of 7350, with 75 per cent neutrophils. The fasting blood sugar was 107 mg., the nonprotein nitrogen 31 mg., the total protein 6.9 gm., the albumin 4.9 gm., the globulin 2.3 gm., the alkaline phosphatase 2.5 units, the bilirubin 2.4 mg.,

the cholesterol 221 mg., and the cholesterol esters 137 mg. per 100 cc. The prothrombin time was 100 per cent. Thymol turbidity was 1 unit, and cephalin flocculation was negative. The serum cholinesterase was 0.99 delta pH units per hour. A bromsulfalein test demonstrated 27 per cent retention of the dye. The serum lipase was 176 Russell units. A stool was guaiac negative and contained no obvious muscle fibers or increased fat. Gastric aspiration showed abundant free hydrochloric acid; a smear of the sediment was negative for tumor cells. A tuberculin skin test was negative. A Graham–Cole test revealed that the gall bladder filled well, and no calculi were seen. A Cholografin study did not outline the biliary ducts, but the gall bladder was filled with dye and no calculi were observed; the gall bladder contracted well after a fatty meal. A barium-enema examination was considered negative, and a barium-meal examination outlined a normal upper gastrointestinal tract. A film of the chest was normal, as was an intravenous pyelogram. An examination by a gynecologist was noncontributory.

During the hospital stay the patient progressed satisfactorily. The temperature remained within normal limits. The serum amylase on the ninth hospital day was 132 Russell units, and the bilirubin 0.8 mg. per 100 cc.; the bromsulfalein test showed 30 per cent retention of the dye. Four days later the serum amylase was 57 Russell units, and the bilirubin 0.7 mg. per 100 cc. On the twentieth hospital day the bromsulfalein test showed 17 per cent retention of the dye; the lipase was 1.2 cc., and the serum amylase was 56 Russell units, and the bilirubin 0.6 mg. per 100 cc. On the twenty-seventh hospital day the amylase was 45 Russell units, the bilirubin 0.5 mg., and the alkaline phosphatase 3.3 units per 100 cc., and the bromsulfalein test showed 10 per cent retention of the dye. Duodenal drainage contained many bile-stained cells, but neither cholesterol nor calcium bilirubinate crystals were seen. On the thirty-first hospital day an operation was performed.

Differential Diagnosis

Dr. Victor G. Balboni*: Before beginning the differential diagnosis, I should like to see the x-ray films.

Dr. John F. Gibbons: I have selected a few films from various examinations. The first films of the chest give no evidence of pulmonary disease, and the heart is not enlarged. The gastrointestinal examination is apparently negative; there is no evidence of duodenal abnormality or displacement. The intravenous pyelogram reveals no urinary-tract disease. A routine Graham–Cole test with Priodax demonstrates that the gall bladder elaborates the dye very well and shrinks after a fatty meal. No stones are seen. After the intravenous pyelogram Cholografin was given in an attempt to outline the biliary tree; the gall bladder filled after about two hours and shrank down after a fatty meal, indicating good function, but there was not enough concentration of medium in the bile ducts at any one time to outline them.

Dr. Balboni: Do you see any evidence of gastritis or duodenitis?

Dr. Gibbons: No; but gastritis could be present without being recognized.

Dr. Balboni: Are there any areas of calcification in the upper abdomen?

Dr. Gibbons: No.

Dr. Balboni: To summarize, this forty-six-year-old woman had had recurrent attacks of epigastric pain. This pain had a bizarre radiation — to the back, down over to the right side and into the lower quadrant. The dark stools noted before entry were presumably due to blood in the gastrointestinal tract; this was confirmed by the fact that she actually vomited blood before entry. On admission the liver apparently was slightly enlarged, and there was some vague tenderness around and to the right of the umbilicus. Laboratory studies revealed subclinical jaundice — the bilirubin was 2.4 mg. per 100 cc., and the bromsulfalein excretion was definitely prolonged, but the cephalin flocculation, thymol turbidity and urinary urobilinogen were all normal. She therefore had some form of obstruction to the biliary tract.

In any patient who has recurrent pain in the upper abdomen, we have to consider coronary-artery disease, duodenal ulcer, retroperitoneal cancer and possibly even renal disease. These hypotheses, which are raised by the history, cannot be confirmed on physical examination or laboratory studies, and I mention them merely to eliminate them from the discussion.

The crux of this case seems to be, What was the cause of the biliary obstruction? Did the patient have gallstones? Certainly, the history suggests gallstones. She had intolerance to fatty foods and a striking weight loss because she had limited her diet to avoid discomfort. The Graham test, however, was negative; no stones were seen in the gall bladder. I believe that there are a certain number of cases in which small stones in the gall bladder have been missed by the radiologists, but those cases are rare. In addition the biliary drainage failed to reveal cholesterol or bilirubinate crystals. This is an excellent test and is usually positive if gallstones are present. It is also usually positive in cholesterolosis of the gall bladder without any frank stones that can be seen with the Graham–Cole test. Therefore, because of the negative Graham test and the negative biliary-drainage examination, I find it difficult to assume that she had gallstones; moreover, I do not believe that gallstones could account for the attacks of pain.

Pancreatitis is the other possibility that is always seriously raised in cases of pain in the upper abdomen. The serum amylase on entry was 176 Russell units. Other conditions in the upper abdomen may give rise to an elevated serum amylase but rarely to a level of 176 Russell units. Originally, we were taught that

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pancreatitis was almost invariably associated with gallstones, a stone presumably being impacted in the ampulla of Vater and causing reflux of bile into the pancreas, with resulting pancreatitis and release of pancreatic enzymes into the pancreas itself. More recently figures have been accumulated to show that gallstones are found in no more than 40 per cent of the cases of pancreatitis.[1] Therefore, it is not necessary to assume that she had gallstones if she had pancreatitis. Pancreatitis may be acute and fulminating and associated with shock and severe pain in the upper abdomen, or it may be mild, running a chronic recurring course quite similar to this patient's. Melena and hematemesis, both of which she had, may occur in pancreatitis, presumably owing to associated gastritis and duodenitis.[2] Biliary obstruction is common in pancreatitis and is probably caused by pressure on the common duct as it passes over or through the head of the pancreas. Enlargement of the liver and sometimes even enlargement of the spleen may occur, perhaps as a result of obstruction of the duct or of actual inflammation in the liver, a hepatitis. The white-cell count may be elevated, or it may be normal, as it was in this case. The prolongation of the bromsulfalein test is more difficult to explain, but I think that a bromsulfalein test is not of much diagnostic value in the presence of biliary obstruction of any degree. This patient probably had partial biliary obstruction. The bromsulfalein test is useful in following the course of the patient but is not in itself diagnostic.

The operation that was performed on the thirty-first hospital day, I assume, was to explore the pancreas and common duct for possible stones or possibly stenosis of the duct. I predict that no gallstones were found but that pancreatitis was. My diagnosis is idiopathic chronic recurrent pancreatitis, with no primary biliary disease.

DR. WARREN POINT: How do you account for the normal alkaline phosphatase?

DR. BALBONI: In partial biliary obstruction one would expect the alkaline phosphatase to be elevated; however, it is not uncommon to find one or more of the liver-function tests out of line with the others.

DR. ALFRED KRANES: Do you think the patient had attacks of pancreatitis every time she had one of the episodes of abdominal pain?

DR. BALBONI: I think the more severe ones that lasted four or five days were due to pancreatitis.

DR. CHARLES H. DU TOIT: I saw this patient on the ward; I should like to clarify some points of the history. She had pain of some degree every day she was in the hospital. I did not get the impression that there were prolonged episodes of severe pain although I believe that pain had been somewhat worse before admission.

DR. BALBONI: In chronic recurrent pancreatitis there may be a stenosis of the common bile duct, which may cause discomfort daily on eating, with some dysfunction of the biliary tract in the absence of stones.

DR. WINFIELD S. MORGAN: Dr. Du Toit, will you tell us the opinion on the ward?

DR. DU TOIT: Our opinion was more or less the same as Dr. Balboni's. I think we considered stones more prominently than he did. This was one of the reasons we advised an operation.

CLINICAL DIAGNOSES

Cholelithiasis.
Subacute pancreatitis.

DR. VICTOR G. BALBONI'S DIAGNOSIS

Idiopathic chronic recurrent pancreatitis.

ANATOMICAL DIAGNOSES

Cholelithiasis and choledocholithiasis.
Probable chronic pancreatitis.
Chronic cholecystitis.

PATHOLOGICAL DISCUSSION

DR. MORGAN: At operation there were many small pigment stones in the gall bladder and one in the duct at the ampulla of Vater. The duodenum was opened, and a sphincterotomy was performed. The common duct was small and thin, without any evidence of dilatation, but a biopsy of the sphincter of Oddi showed chronic inflammation. On palpation of the pancreas, the head and body were woody, and the surgeon believed that there was a pancreatitis of a subacute or chronic type. Unfortunately, no biopsy was taken.

DR. POINT: This case illustrates that dependence on laboratory tests may lead one astray. The clinical picture was more consistent with pancreatitis and with gallstones than the laboratory tests would have one believe. The negative gall-bladder series, the proper filling of the gall bladder in the cholangiogram and the normal alkaline phosphatase were all misleading and brought about a long delay in treatment. The clinical picture was most compatible with continuing inflammation of the biliary-pancreatic system. With that in mind, despite the fact that there was no objective evidence for stones, only the clinical impression that she probably did have stones, the operation was performed. The laboratory tests, including the biliary drainage, were against the diagnosis of stones, which were nevertheless present.

The alkaline phosphatase is thought to be almost of necessity elevated in the presence of partial or complete obstruction. As Dr. Balboni pointed out, that is not so. I should think that the bromsulfalein retention was of the same mechanism as the alkaline phosphatase.

DR. KRANES: We had 2 patients several years ago who had no jaundice but had typical attacks of biliary colic. The bromsulfalein test after an attack went up to 50 or 60 per cent and did not go down to

normal for weeks. This is a study that is not commonly done.

DR. POINT: I agree; I am just saying the bromsulfalein retention and elevated alkaline phosphatase in obstructive jaundice usually, but not necessarily, go together even in the absence of jaundice.

DR. KRANES: It is interesting that the bromsulfalein retention can go so high in the absence of any clinical biliary obstruction. There must be interference with the ability of the liver to excrete the dye.

DR. POINT: The bromsulfalein excretion may be impaired in the presence of obstruction or severe liver-cell disease.

DR. KRANES: Is the obstruction biliary?

DR. POINT: Most probably it is increased pressure in the biliary tree. Very frequently a partial degree of biliary obstruction — too slight to cause jaundice — causes an elevation of the bromsulfalein retention and alkaline phosphatase. This patient must have had enough elevation of pressure from the pancreatitis or stones, or both, to bring about increased bromsulfalein retention without producing the increase in the alkaline phosphatase. What I am trying to say is that she probably had partial obstruction to the biliary tract and yet did not have enough to elevate the bilirubin or alkaline phosphatase.

A STUDENT: Was the appearance of the liver noted?

DR. MORGAN: It was normal on gross inspection.

DR. POINT: None of the liver-function tests that deal with hepatocellular functions alone showed any signs of liver disease, and the spleen was not enlarged.

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CASE 41022

PRESENTATION OF CASE

An eighty-three-year-old man was admitted to the hospital because of difficulty in swallowing.

The patient was known to have had a pharyngoesophageal diverticulum for many years, but this had caused only minimal difficulty until the present episode of dysphagia two months before admission. For the week before admission, dysphagia had become particularly acute, with choking spells and regurgitation of all solid food. Since the dysphagic episode there had been a concurrent weight loss attributable to the progressive inability to ingest food. Three days before admission he suddenly experienced an attack of dyspnea, cyanosis and an urge to defecate, which was not relieved by half an hour at the toilet.

The past history was brief. A transurethral prostatectomy had been performed three years previously with a bilateral orchiectomy. Coincident with this hospitalization there was an attack of phlebitis in the lower extremities, and the patient had worn elastic stockings ever since. There was no history of claudication. In the recent past he had been treated for apparently mild cardiac decompensation with digitalis, which was discontinued five days before admission.

Physical examination revealed an alert man with signs of obvious weight loss. The pharynx was injected but nonpainful. The chest was emphysematous, and a few crepitant rales were heard at the lung bases. The heart was considered slightly enlarged; the rhythm was regular, and a Grade 2 systolic murmur was heard at the apex and base. Abdominal examination was negative. The testicles were absent. Only a small amount of prostatic tissue was palpable by rectum. No calf tenderness could be elicited. There was slight pitting edema of the legs.

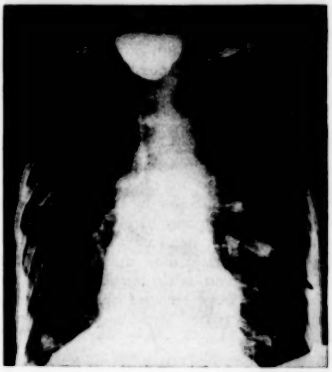

FIGURE 1. *Posteroanterior Film of the Chest, Showing the Large Pulsion Diverticulum of the Proximal Esophagus Outlined with Barium.*

A patch of increased density is present in the lingula (arrow). The lungs are emphysematous, and there is a paucity of vessel markings on the right, particularly in the upper-lung field.

The temperature was 98.6°F., the pulse 80, and the respirations 20. The blood pressure was 128 systolic, 90 diastolic.

Urinalysis was negative. Examination of the blood showed a total protein of 6.3 gm. with an albumin-globulin ratio of 1.6 and a nonprotein nitrogen of 32 mg. per 100 cc., a potassium of 3.7 milliequiv., a sodium of 132 milliequiv., a chloride of 88 milliequiv. and a carbon dioxide of 28 milliequiv. per liter. Fluoroscopic study of the chest disclosed emphysema and changes in the left lingular segment interpreted as possible pneumonitis (Fig. 1). A barium-swallow examination demonstrated great difficulty in swallowing that was due to a dilatation of the upper esophagus, and a large pharyngoesophageal diverticulum with very little barium passing into the stom-

ach. An electrocardiogram showed a normal rhythm at a rate of 95, a PR interval of 0.14 second, a normal axis and one premature ventricular beat; the T waves were flat in Lead 1, low and upright in Leads aVL and V_1, diphasic in Leads V_2 through V_6 and low and diphasic in Leads 2, 3 and aVF; the ST segments were depressed in Leads 2, 3, aVL and V_2 through V_6.

An esophagoscopy was performed and the diverticulum emptied by suction, but a feeding tube could not be placed. Intravenous feedings were given in preparation for surgery. Removal of the diverticulum was considered too hazardous at the time, and an interim gastrostomy under local anesthesia was contemplated. However, in the evening of the seventh hospital day, the patient suddenly had an attack of dyspnea, cyanosis and tachycardia (rate of 140 per minute). There was no associated chest pain, cough or hemoptysis. His status improved in an oxygen tent, and, shortly after the episode, he exhibited almost normal color, moderate orthopnea, flat neck veins, sighing respirations, a pulse rate of 132, with occasional dropped beats, and a blood pressure of 120 systolic, 80 diastolic. He was given Cedilanid intravenously. An electrocardiogram the next day, in comparison with the one taken the day before, showed some increase in ventricular irritability with a faster heart rate (130). The ST-segment and T-wave abnormalities were slightly more marked in Leads 2, 3, aVF and the leads on the left side of the chest, but the T waves were more upright in those on the right. Blood studies revealed a hemoglobin of 17.1 gm. per 100 cc. and a white-cell count of 19,000, with 92 per cent neutrophils. Two days after the acute episode of dyspnea the patient's condition was fairly good. The heart rate was 100 and regular, and there was no noticeable change in the heart sounds. The neck veins were distended, and the lungs clear to auscultation. The temperature was 101°F., and antibiotic therapy was initiated. Blood studies showed a hemoglobin of 15.1 gm. per 100 cc., a hematocrit of 49 per cent and a white-cell count of 11,400, with 89 per cent neutrophils.

A gastrostomy was performed on the ninth hospital day; tube feedings were begun to supplement parenteral fluids and electrolytes. On the eleventh hospital day, the patient was described as looking "badly." He was restless, with sighing respirations of 32 per minute. The temperature was 100.6°F., and the pulse regular at 112. The white-cell count was 18,800, the potassium 4.9 milliequiv., the sodium 129 milliequiv., the carbon dioxide 23 milliequiv., and the chloride 94 milliequiv. per liter, and the nonprotein nitrogen 51 mg. per 100 cc.; the pH was 7.55. Over the next three days, the clinical status showed little change, with a persistence of fever, leukocytosis, dyspnea and tachycardia. On the fourteenth hospital day an electrocardiogram indicated no significant change except for "a little less sagging than was previously recorded." On the fifteenth day the right calf was noted to be somewhat swollen and warmer than the left but without tenderness. Dicumarol medication was begun. An x-ray film of the chest taken with a portable machine on the next day showed no change from the examination two weeks previously. The patient's condition over the last week gradually deteriorated, with little change in symptoms or physical findings. No definite evidence of calf tenderness or a Homans sign could ever be elicited. He spent most of this final week of life in an oxygen tent with borderline cyanosis and complained constantly of dyspnea. During this period, owing to constantly subnormal values of blood chloride and sodium, sodium chloride solution was administered by gastrostomy tube. The abdomen was silent for two days, but a soft stool, which was guaiac negative, was later passed. The gastrostomy wound healed without incident. The urinary output remained over 1000 cc. a day throughout the course. A blood culture was reported as negative. He died on the twenty-first hospital day.

Differential Diagnosis

Dr. Evan Calkins*: Did this patient have oral feedings while in the hospital?

Dr. John T. Quinby: No; he did not.

Dr. Calkins: Was the hemoglobin elevated on admission?

Dr. Quinby: No; that elevation was a single reading that was not subsequently confirmed.

Dr. Calkins: May we see the x-ray films?

Dr. C. C. Wang: Examination of the chest on admission (Fig. 1) reveals considerable pulmonary emphysema; the right-upper-lung field is more radiolucent than the corresponding part on the left side. In the right upper lobe the blood vessels are sparse and inconspicuous; the right hilar shadow is not enlarged, however. There are areas of ill defined increased density in the right-midlung field and in the lingular segment of the left upper lobe. A film of the chest taken with a portable machine about two weeks after admission shows a progressive increase in the prominence of the densities in both lung fields. The heart appears somewhat enlarged, and the aorta is quite tortuous. A barium-swallow examination demonstrates a large pharyngoesophageal diverticulum. There is very little barium in the stomach.

Dr. Calkins: The lingular consolidation does not appear to be too conspicuous.

Dr. Benjamin Castleman: Has it changed at all?

Dr. Wang: The lesion in the left upper lobe shows very little change. There is some increase in size in the density in the right-midlung field in two weeks' time.

Dr. Calkins: Usually in these discussions and, if possible, in practice, one tries to single out quickly the salient features of the case and then determine how they can be best put together. This eighty-

*Assistant in medicine, Massachusetts General Hospital.

three-year-old man, in whom one expects to find a number of more or less incidental ailments, does not disappoint us. By history or by extrapolation from the findings on admission, we discover that he had had a transurethral prostatectomy and at the same time an orchiectomy, which should indicate a carcinoma of the prostate. There was evidence of heart disease with congestive heart failure in the past, a slightly enlarged heart and changes in the electrocardiogram, which I interpret as nonspecific evidence of myocardial damage. In the absence of hypertension the most reasonable explanation for those findings is coronary-artery disease. There was some evidence of renal disease, with albuminuria, but the urinary concentration was good and the nonprotein nitrogen was not elevated on admission. The pulmonary emphysema is a conspicuous feature; whereas the first findings that I mentioned can be put in the background, I think that the pulmonary emphysema is a major factor, as evidenced on physical examination and by the elevated carbon dioxide. That the x-ray films showed a radiolucent area at the right apex brings the pulmonary picture even more into focus and makes me wonder whether there was an emphysematous bleb in that area.

DR. WANG: It does not look like a bleb.

DR. CALKINS: Finally, the patient had a pharyngoesophageal diverticulum that had all the characteristics of a Zenker diverticulum. It usually occurs in older patients, chiefly men, and increases in size, often with the development of choking and other obstructive symptoms as this patient showed. Two frequent complications are terminal infection and carcinoma of the pouch. Finally, it should be mentioned that this elderly man came into the hospital and very probably went to bed, resulting in various complications, including possibly phlebothrombosis. The swollen left leg supports this possibility.

The primary problem appears to be pulmonary and superimposed on this complicated background. The sudden attacks before admission and the one shortly after admission represent the key points in this presentation. They were manifested by a rapid onset of dyspnea and cyanosis, with tachycardia, especially in the second attack. The urge to defecate was probably a reflex phenomenon. The attacks were apparently of short duration in themselves, but were followed by progressive deterioration, with striking dyspnea, cyanosis, leukocytosis and fever.

In trying to tie these conditions together, I think first of pulmonary embolism. The staff apparently was also particularly concerned about this possibility. The sudden onset of the attacks, the relatively speedy improvement as the reflex spasm subsided and the conspicuous cyanosis, without obvious manifestations on auscultation of the lung or in the x-ray film, are consistent with pulmonary emboli without infarction, as is the swelling of the leg. The absence of pain, cough and hemoptysis are somewhat against this possibility.

The second possibility I think I ought to consider is aspiration of material from the diverticulum of the esophagus. That is why I asked if the patient had been fed by mouth when he came into the hospital. The fact that he had not eaten makes this less likely. I should be interested in knowing whether the neck veins were distended on admission because, perhaps naïvely, I wonder whether the pouch or diverticulum could have caused such a distention and whether their flattening, in association with the acute episode, indicated emptying of the diverticulum into the bronchus. Pursuing those lines, one would have to visualize that a bolus of food, initially lodging in the trachea or bronchi, then broke up and settled in the finer radicles of the pulmonary tree, causing the chronic pulmonary disease with the failing course. The absence of cough or choking at the time of this episode is against that possibility. The location of the shadow on the x-ray film is also somewhat against it.

There are other possibilities, but they seem remote. A ruptured bleb might also explain this sudden episode, but the x-ray film was not characteristic of that and the recovery was too rapid. The diverticulum might have ruptured or herniated into the thorax, but that does not seem too likely. If one looks at the situation in more piecemeal fashion the acute episodes may have represented primary tachycardia, but the tachycardia was not very significant clinically. A ball-valve thrombus in the left atrium could account for an episode of this sort, but the patient was not said to prefer sitting up and that, of course, does not fit in with the rest of the picture. Acute myocardial infarction may have been the explanation, but I think that this story was one primarily of lung — not heart — disease.

If one focuses on the inexorable course of the pulmonary disease, pulmonary fibrosis comes to mind. The acute diffuse interstitial fibrosis described by Hamman and Rich[1] is a fulminating disease taking place in weeks or months, characterized by marked dyspnea and cyanosis, similar to that displayed by this patient, and showing on histologic examination edema, necrosis and fibrosis of the alveolar wall. This would explain the striking pulmonary symptoms, without too much evidence on x-ray examination, but does not fit the over-all picture. It would be too much of a coincidence to superimpose it on the other difficulties. Chronic fibrosis, perhaps the result of tuberculosis, is a very remote possibility. There was no history of silicosis or beryllium intoxication. Scleroderma will produce chronic pulmonary crippling without too much to show in the x-ray films. I do not know of any case in which scleroderma of the esophagus has been associated with diverticulum formation, but the myocardial, pulmonary and kidney diseases could have been linked together on this basis. I do not think that is likely, however.

In passing I should like to mention the electrolyte situation. The persistence of a low sodium and chloride despite the administration of salt by gastric tube

makes me wonder whether this was the pulmonary hyponatremia that has been described in association with tuberculosis[2]; in 1 of the original cases described by Winkler and Crankshaw[3] it was associated with carcinoma of the lung. I have not heard about it in other diseases.

I am going to have to choose between aspiration in association with the pouch of the esophagus, pulmonary infarcts and progressive pulmonary fibrosis as described by Hamman and Rich.[1] Of those possibilities I shall select aspiration as the cause of the progressive pulmonary disease. It fits the over-all picture as well as anything. I shall make the further diagnoses of senile emphysema and coronary-artery disease and raise the possibility of pulmonary hyponatremia.

DR. ALFRED KRANES: How do you explain the paroxysmal nature of the symptoms on the basis of aspiration?

DR. CALKINS: It is unfortunate for my case that there was not more choking with those paroxysms. Certainly, a discharge of secretions from the esophagus would produce paroxysmal pulmonary symptoms; secondary infection behind the obstructed bronchioles might have caused the deteriorating course. Against this interpretation is the fact that choking was not conspicuous, and apparently, at the time of barium-swallow examination, the obstruction was complete.

DR. CASTLEMAN: What, exactly, do you mean by aspiration — aspiration of the contents of the diverticulum, an aspiration pneumonia?

DR. CALKINS: Acute episodes of obstruction with fragmentation of the bolus, and its dispersion into the small bronchioles with aspiration pneumonia.

A PHYSICIAN: Are the x-ray films of the lung consistent with cystic disease?

DR. WANG: I do not think so. The lung fields are very emphysematous. The one finding that takes our attention is marked radiolucency of the right-upper-lung field, with a decrease in prominence of the blood vessels. A couple of weeks ago, when Dr. Laurence L. Robbins and I reviewed this case, he mentioned the possibility of pulmonary arterial thrombosis and infarction in the peripheral lung field on the right side.

DR. CASTLEMAN: Dr. Kranes, I gather that you think those episodic areas meant something like pulmonary infarction.

DR. KRANES: Pulmonary infarction and emboli.

DR. CASTLEMAN: Dr. Ropes, have you a comment?

DR. MARIAN W. ROPES: I thought the diagnosis of pulmonary emboli sounded more likely although the evidence is not clear cut.

CLINICAL DIAGNOSES

Pulmonary embolus.
Esophageal diverticulum, with obstruction.

DR. EVAN CALKINS'S DIAGNOSES

Aspiration pneumonia.
Diverticulum of esophagus, with obstruction.
Senile emphysema.
Coronary-artery disease.
?Pulmonary hyponatremia.

ANATOMICAL DIAGNOSES

Pulmonary embolism, massive, on right, with organization.
Pulmonary fibrosis and emphysema.
Cor pulmonale.
Pulmonary infarcts, healed.
Pulmonary embolization, chronic.
Chronic lipid pneumonia, aspiration.
Thrombophlebitis, right, popliteal vein.

PATHOLOGICAL DISCUSSION

DR. CASTLEMAN: At autopsy the heart was moderately enlarged, most of the enlargement being on the right side. That the right ventricle was about twice the normal thickness without any disease of the mitral valve indicates that this was probably due to the lung disease, a cor pulmonale. The lungs were large and emphysematous and had a great deal of fibrosis on gross inspection. In the main right pulmonary artery we found a large thrombus or embolus that was adherent and extended quite a distance into the right lung; part of it extended back into the main pulmonary artery. We also found smaller emboli in the left pulmonary artery further in the lung. This would account for the decrease in vascular markings on the x-ray film mentioned by Dr. Wang. The large embolus seemed well organized and probably occurred the day before admission — that is, it is consistent with an age of about three weeks' duration. In the lungs there were also some small infarcts that were quite old. The lesion that Dr. Wang described in the lingula on the left that did not change proved to be something akin to what Dr. Calkins predicted — chronic lipid pneumonia, an aspirative process that would be very likely to occur in a person with an esophageal diverticulum. There were several areas of lipid pneumonia that probably contributed to the insufficiency of the lung. Most of the insufficiency was probably due to the combination of the emphysema and old infarcts. Throughout the lungs were many recanalized vessels, indicating that the patient had been having recurrent embolization adding to the insufficiency of the lungs and producing the right-sided heart failure. The source of the emboli was a thrombus in the right popliteal vein. The prostate gave no evidence of carcinoma. There was a slightly enlarged median bar, which was perfectly benign.

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TRANQUILIZING AGENTS

In the past two years certain new drugs, which for want of a better term have been called tranquilizing agents, have appeared. These substances, unlike the barbiturates and other soporific drugs, are not depressant to the higher cortical centers but apparently act through what appears to be an alteration of the functions of lower centers, perhaps in the region of the hypothalamus. The two most effective tranquilizers are *Rauwolfia serpentina* and chlorpromazine.

R. serpentina, a drug known to Indian physicians for many years and successfully employed by them to quiet their excited and hypertensive patients, has a long history of clinical use. Although it was first described over two hundred years ago, it received almost no attention from the medical world outside India, where many favorable observations were made by physicians. Undoubtedly, an article in 1949 by the distinguished Indian physician, Rustom Jal Vakil,[1] describing its action in hypertension, did much to attract attention to the agent. Since then many investigators have been interested in this substance. Chemists have crystallized several compounds from the original extract and recently ascertained the structure of one of the very active principles, reserpine. Pharmacologists have found it to be a most interesting substance with manifold actions. It slows pulse rate, lowers elevated blood pressure and calms excited, agitated patients without any severe degree of sedation. It brings about a tranquil state in which events or things that otherwise would be irritating or even obnoxious are no longer of so much importance. *Rauwolfia serpentina* and now the crystalline principle, reserpine, have been used successfully in the treatment of hypertension, first by many Indian physicians and more recently in this country by Wilkins and Judson.[2] It is at present considered one of the more useful agents in this field and is widely employed for the treatment of mild hypertension. More fascinating and of equal importance is its administration to agitated, excited, hypomanic and manic patients, on whom its soothing, tranquilizing effect is most helpful.[3] It is too early to appreciate fully the role of this drug in psychiatry, but from what information is already available, it has created a great deal of interest and has opened another line of approach to the treatment of certain types of patients.

Chlorpromazine, like Rauwolfia, is characterized by a variety of useful therapeutic actions. This substance was synthesized by chemists of Rhône–Poulenc Specia, a French pharmaceutical laboratory, who were looking for a more effective antihistaminic agent. It is chlorinated phenothiazine closely related to the antihistamine, Phenergan, and the agent used in Parkinsonism, Diparcol. French pharmacologists soon observed several exceptional properties in this drug. It was an effective antiemetic that blocked the effect of apomorphine in animals; the action of narcotic analgesics, sedatives and anesthetics was

potentiated. Like Rauwolfia, it brought about relaxation without any degree of sedation.

Psychiatrists discovered that chlorpromazine had a powerful tranquilizing effect on highly agitated, excited or manic patients.[4] The French surgeons, Laborit et al.,[5] found it a most useful agent in hibernation therapy. They believed that it brought about smoother anesthesia and at the same time prevented shock. In this country Friend and Cummins[6] reported it to be a powerful antiemetic agent capable of abolishing nausea and vomiting from a wide variety of causes. These workers also described its highly useful effect in a patient with chronic alcoholism, who lost his agitated, tremulous, excited state during the drying-out period if he was given adequate amounts of the drug.[7] This tranquilizing effect has more recently been extended to the withdrawal of narcotics and barbiturate drugs. It is also very useful in calming the agitation of elderly, senile, arteriosclerotic patients, who at times develop fixed ideas or patterns of action that are often harmful. Frequently, these unhappy persons calm down and are able to lead a much more normal existence.

These agents have opened an entirely new and very interesting field of study. Undoubtedly, more effective substances with a similar action will soon be developed. It is impossible as yet to ascertain with certainty just where these compounds act on the central nervous system. The tranquilizing effect is not like that of the barbiturates or other sedatives. There appears to be very little higher-center or cortical depression, even when large doses are given. The patient can be readily aroused and is capable of carrying on normal functions in an intelligent manner. If the drugs are pushed farther, there is no dramatic deepening of the tranquilizing effect or further sedation like that which occurs when the barbiturates are pushed but only an increased duration of the desired reaction.

Both agents also have undesirable features. An interesting reaction, which occurs infrequently, is the refusal of certain persons to submit to the tranquilizing effect. Instead of relaxing and accepting a calm, tranquil state, they become most uncomfortable, resist the action of the drug and frequently refuse further medication. In other words, they refuse to be tranquilized, perhaps because the sensation is foreign to their usual natures.

Rauwolfia, fortunately, seems to be fairly free of serious toxic effects. It causes nasal congestion, which leads to an occasional epistaxis and rarely inflammation of the sinuses; there is some increased irritability of the gastrointestinal tract, which in patients with an irritable colon can cause considerable annoyance. Lastly, Rauwolfia apparently predisposes some persons to an increase in dream fantasy, which may be so real or of such intensity as to create considerable sleep activity and even nightmares. Generally, however, the drug is well tolerated, and it increases the patient's sense of well-being and appetite, with an increase in weight unless care is taken.

Chlorpromazine, like Rauwolfia, is usually well tolerated by the vast majority of patients. It can produce drowsiness, which commonly passes off as the drug is continued. Care must be taken when it is given parenterally, since orthostatic hypotension develops in some cases. This is usually mild but can be severe. Assuming a recumbent position with elevation of the feet is ordinarily sufficient to overcome this effect. The most serious reaction is the appearance of jaundice in a small percentage of patients who are given the drug for two weeks or more. This is an obstructive type of jaundice, and liver biopsies have shown no serious degree of parenteral involvement. The jaundice clears promptly once the drug is withdrawn. The mechanism of this reaction is not at present known.

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PLOTTING THE WEATHER MAP

THE importance of weather and climate as they affect practically all human activities has already been noted. Not only do they have their impact on commerce and agriculture, on the various aspects of business, and on travel by land and sea and in the air, with outdoor recreation almost completely dependent on them; they also affect physical health and emotional well being and supply the world's most dependable topic of conversation.

It is not merely that the weather is changeable, — a matter commonly appreciated, — but as records accumulate and history's habit of repeating itself is better recognized there has come the realization that climate, too, is a flexible and fluctuating commodity. These fluctuations succeed each other in cycles of varying length and intensity, from the minor wet- and-dry oscillations of a few years' duration to the mighty changes that are suspected of having been responsible for the slow tidal advances and recessions of the polar ice caps.

On a minor scale the experiences of the past unprecedentedly wet summer, with its aberrant winds, have shown how intemperate the weather can be, even in the temperate zone, and have emphasized the need for reliable predictions.

In view of this universal preoccupation with the weather and the desirability of having it accurately predicted, *Science*, in its issue of November 12, 1954,

has presented a brief account, by F. W. Reichelderfer, its chief, of the history, the operation and the future goals of the United States Weather Bureau.

The violence of the year 1869, when nearly 2000 vessels were wrecked or sunk on the Great Lakes alone, led Congress to establish a national weather service to give "advance notice of the approach and force of storms." As a result of the service, which has been steadily improving during the nearly eighty-five years of the Bureau's existence, the loss of men and ships has declined to the point where the death toll of hurricanes is now less than 2 per cent of the lives sacrificed a quarter of a century ago. Over the years, according to this authentic source, the Bureau has served notice of "blizzards, cold waves, ice storms, crop-damaging frosts, and floods; recently progress has been made in issuing timely warnings on the smallest, most elusive, and most furious storm of all — the tornado."

The Bureau maintains 300 local offices for the collection, processing and dissemination of weather information. In addition it has 18 centers for general forecasting, 31 for aviation forecasting, 87 river district offices, 7 centers for river forecasts, 43 climatologic centers and 3 for weather-records processing. Further information is supplied by more than 11,000 substations, manned in general by unpaid observers. Seeking in no way to compete with the picturesque long-range weather-prediction service of the *Old Farmer's Almanac*, with its far-seeing weather eye, the Bureau has as yet found no reliable method of extending weather outlooks beyond thirty days; further research is necessary in this aptly termed "zone of overlap" between weather and climate.

Oracles who rely for their knowledge of the weather on the length of corn tassels, the state of squirrels' tails, the thickness of wild-cherry bark, the size of a goose's breastbone, the color of the woolly caterpillar and the bullet in grandpa's leg will view with scorn the scientific gadgetry on which the educated meteorologists are forced to depend. These include cloud physics, the study of atmospheric electricity and atmospheric pollution, high-speed digital computers, solar, sky and terrestrial radiation, radar meteorology and automatic weather observation.

Absolute accuracy is not yet obtainable, but the record is constantly improving, for it is increasingly necessary to know when storms rise swiftly o'er the deep and the harbor bar is moaning.

CONFERENCE ON ALCOHOLISM

THE sixth Conference on Alcoholism, to be held at John Hancock Hall, Boston, in the afternoon and evening of January 26, marks not only continued progress in the study and control of this major problem, but also the tenth anniversary of the establishment of the Boston Committee on Alcoholism.

The program is planned to attract a public audience of varied interests; the conference is being held not only under the auspices of the Boston Committee but under the sponsorship of more than fifty industries, unions, businesses and professional groups. The importance of the relation between industry and alcoholism will be featured in a special industrial session. General chairman for the conference is Dr. Robert Fleming, of Boston, with Albert B. Carter, state commissioner of probation, as program chairman. Prominent among the speakers will be Dr. Robert Collier Page, president of the Industrial Medical Society and chief medical consultant for the Standard Oil Company of New Jersey.

So long as fruits are fermented and alcohol distilled for man's consumption the problem of alcoholism and drunkenness will complicate existence. It will not be solved by prohibition or police action or an excess of piety, but it will gradually be modified and will certainly be most intelligently approached by applying the methods of research, of discussion and of education. Temperance in the use of alcohol will not be achieved by an intemperate attitude on the part of those who seek to abolish its evils; much may be accomplished by accepting and promulgating the counsel of Paul to the Philippians: "Let your moderation be known unto all men."

FRIEDRICH VON MÜLLER AND WILLIAM OSLER

THE death of Friedrich von Müller in Munich in 1941 in the midst of World War II recalled a long medical friendship, which had terminated in 1919, with William Osler's death in World War I. Osler must have been aware of the fine character of the work that Müller was doing long before they met, for references to it had crept into the various editions of his textbook, but it was during the annual German Congress of Internal Medicine in Munich in 1906 that their friendship ripened. Two years later, Müller was president of the Congress, held in Vienna, and Osler, accompanied by Joseph H. Pratt, of Boston, again attended and reported on the highlights to his American colleagues in the form of a letter to the *Journal of the American Medical Association*.

In 1911 there was much discussion in medical circles regarding the use of full-time physicians as teachers in medical schools, as recently adopted at the Johns Hopkins Hospital. A royal commission was set up in London to examine the evidence, and Müller was asked to give testimony. He was strongly opposed to the "whole-time scheme," for he was convinced that all teachers ought to be also in the practice of medicine. It may well have been that Osler was the instigator in inviting Müller to London; it would have been characteristic of him to welcome the leader of German medicine as a contributor to the discussion. At all events his Munich contemporary stayed at Osler's home in Oxford during part of his

visit, and plans must have been hatched at that time for the London International Congress of Internal Medicine, to be held in 1913, with Osler, now Sir William, as president of the medical section. During that meeting, Müller, with his wife and daughter, were Osler's guests at Brown's Hotel in London, and the German internist was one of the stars of this famous congress, held when the peace of Europe was already disturbed and World War I was only a year away. The next Congress was planned for Munich in 1917, with Müller as president, but war made that meeting impossible.

Even after war started in August, 1914, Osler, in spite of the hostile anti-German atmosphere of Oxford, could not turn against his friend of such long standing. Word came through from Müller in 1915, by a friend in common, Arnold Klebs, in Switzerland, and Osler sent an affectionate reply. Revere, his son, deep in the muck of trench warfare, carried Osler's letter to Müller, to be used in case Revere was captured. Faith held to the end, for, in Osler's mind, medicine knew no boundaries and war could not change his deep-seated admiration for his associate, even though he came from an enemy country. Both held the same high ideals; both exemplified the best qualities of teachers, and both were respected and admired by the keenest of critics, the contemporary students of medicine.

Connecticut Medical Society. — *With the growth and development of the country, institutions, which had a small beginning, expand and assume corresponding importance. . . . Among the number that in New England have attained distinction, is the Connecticut Medical Society, which has reached the venerable age of sixty-two years.*

Boston M. & S. J., *Jan. 17, 1855*

MASSACHUSETTS MEDICAL SOCIETY

THOMAS DUCKETT JONES
1899 - 1954

T. Duckett Jones died on November 22, 1954, at the Johns Hopkins Hospital, at the age of fifty-five, of diffuse vasculitis and malignant hypertension. He was born in Petersburg, Virginia, descendant of a colonial family long distinguished in medicine. His father was a physician, his brother is a surgeon, a sister is a physician, and 2 other sisters are married to physicians. He graduated from the Virginia Military Institute in 1919 and received his medical degree from the University of Virginia in 1923, later serving as intern and resident at the University of Virginia Hospital. In 1925 he was Dalton Fellow and cardiac resident at the Massachusetts General Hospital, and thereafter he spent a year as National Research Council Fellow with Sir Thomas Lewis at University College Hospital in London. In 1928 he returned to the House of the Good Samaritan in Boston, where he organized the clinics and the research department, which he directed for the next twenty years. During this period he was also an active member of the faculty of Harvard Medical School and of the staff at the Massachusetts General Hospital, where he inaugurated and developed the rheumatic-fever clinic.

As a result of his many important contributions, he became recognized internationally as an authority on

rheumatic fever. In 1947, because of his eminence in the field, he was asked to become the medical director of the newly established Helen Hay Whitney Foundation in New York City. It was with great reluctance that he gave up his active research career in Boston, but the realization of the opportunity offered by his new duties to further the control and prevention of the disease to which he had devoted his life left him no alternative. In addition to his many responsibilities in this connection, he was a vice-president of the American Heart Association and chairman of its Council on Rheumatic Fever, president-elect of the National Health Council, president of the Protein Foundation and chairman of the Committee on Plasma Fractionation and Related Processes at the Laboratory of Physical Chemistry at Harvard University, as well as an original member of the Advisory Council of the National Heart Institute.

Those who have been in close touch with the activity of Duckett Jones in late years have come to realize his vital impact on the public health of this country. More than any other person he was cognizant of the status of medical research in basic medical science as well as in cardiovascular disease going on throughout the United States. He traveled extensively to many different centers as well as to lesser institutions, and he talked with many persons carrying on research; his invaluable experience and advice were constantly sought by his colleagues, particularly in the various councils and institutes of health, especially the National Advisory Heart Council at Bethesda and Washington. His part in the improvement of child health and welfare was pre-eminent, and he will be greatly missed by both medical and lay persons responsible for the development not only of medical research but also of medical education and the organization of programs to improve the health of the entire nation.

Duckett Jones was in many ways an unusual person. His deep loyalty to his friends, to his associates and to his profession was his religion. His life was devoted to the conquest of rheumatic fever, and through his own efforts and those of countless others whom he inspired he well knew that victory was near at hand. His last important public appearance was as chairman of an international panel on rheumatic fever at the Second World Congress of Cardiology in Washington in September, 1954. It was shockingly evident to his friends at this time that he was seriously ill, but only on their insistence did he finally seek medical aid. He lived only two months longer, but to the end it must have been a source of deep satisfaction to know that the studies he started a quarter of a century ago and the interest he inspired in others elsewhere had played such a significant role in the progress of the intervening years. In Boston alone there are 3000 patients who recall with gratitude and affection his careful and kindly guidance through childhood rheumatism at the House of the Good Samaritan and at the Massachusetts General Hospital.

His was truly a dedicated life.

E.F.B.
H.B.S.
P.D.W.

NOTICES

HARVARD MEDICAL SOCIETY

A meeting of the Harvard Medical Society will be held in the main amphitheater (Shattuck Street entrance), Peter Bent Brigham Hospital, Boston, on Monday, January 24, at 8 p.m.

The program, which will be presented by the Peter Bent Brigham Hospital, Francis D. Moore presiding, is as follows:

Carboxypeptidase and Yeast Alcohol Dehydrogenase, Zinc Metallo-Enzymes. Bert L. Vallee, Peter Bent Brigham Hospital.

Clinical Experiences with 9-Alpha Fluorohydrocortisone. Albert Renold, Najib Abu-Haydar, Alan Goldfien and George W. Thorn, Peter Bent Brigham Hospital.

Symposium on Low-Temperature Physiology and Surgery:

Experiences with the Surgical Application of Hypothermia. Henry Swan, University of Colorado.

Ventricular Excitability Cycle as Influenced by pH and Hypothermia. Albert H. Hegnauer and Benjamin Covine, Boston University.

Early Applications of Hypothermia to Neurosurgery. James C. White, William Sweet, William Lougheed and William Brewster, Massachusetts General Hospital.

Specializations of Hibernators. Charles P. Lyman, Peter Bent Brigham Hospital.

SOUTH END MEDICAL CLUB

A meeting of the South End Medical Club will be held at the headquarters of the Boston Tuberculosis Association, 554 Columbus Avenue, Boston, on January 18 at noon. Dr. Christopher J. Duncan will speak on the subject "Common Gynecologic Problems as Related to the Office." All physicians are invited.

SOCIETY MEETINGS AND CONFERENCES

CALENDAR FOR THE WEEK BEGINNING THURSDAY, JANUARY 20

THURSDAY, JANUARY 20

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*8:45–9:45 a.m. Cardiac Grand Rounds. Yamins Auditorium, Beth Israel Hospital.
*9:00–10:00 a.m. Surgical Rounds. Sherman Auditorium, Beth Israel Hospital.
*9:00–10:00 a.m. Arthritis Grand Rounds. Robert Breck Brigham Hospital.
*10:00–11:00 a.m. Combined Medical-Surgical Rounds. Sherman Auditorium, Beth Israel Hospital.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*11:00 a.m. Thoracic Conference. Pulmonic Stenosis. Drs. Harold Mankin and Dwight E. Harken. Main Amphitheater, Peter Bent Brigham Hospital.
*11:00 a.m.–12:00 m. Medical Staff Conference. Sherman Auditorium, Beth Israel Hospital.
*11:00 a.m.–12:30 p.m. Hand Clinic (Physical Medicine and Rehabilitation Service). Boston City Hospital.
*12:00 m.–1:00 p.m. Surgical Staff Conference. Sherman Auditorium, Beth Israel Hospital.
12:00 m.–1:00 p.m. Staff Conference. Observations with the Electron Microscope on the Structure of the Kidney and Testis. Dr. Don W. Fawcett. Stearns Auditorium, New England Center Hospital.
12:00 m.–1:30 p.m. Teaching Conference. Preëclampsia–Eclampsia. Dr. Benjamin Tenney. New Cheever Amphitheater, Boston City Hospital.
12:15–1:15 p.m. Tumor Clinic. Radiotherapy in Management of Carcinoma of the Cervix. Dr. James Healy. Amphitheater, Peter Bent Brigham Hospital.
*4:00–5:00 p.m. Pediatric Seminar. Burnham Memorial Hospital for Children (Burnham 4), Massachusetts General Hospital.

FRIDAY, JANUARY 21

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*9:30–11:30 a.m. Medical and Surgical Grand Rounds. Drs. George W. Thorn and Francis D. Moore. Main Amphitheater, Peter Bent Brigham Hospital.
*10:00 a.m. Tuberculosis Surgical Clinic. South End Health Unit, 57 East Concord Street.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*11:00 a.m.–1:00 p.m. Medical Grand Rounds. Dr. Proger and Staff. Stearns Auditorium, New England Center Hospital.
*1:30 p.m. Fertility and Endocrine Clinic. Free Hospital for Women, Brookline.
*1:30 p.m. Tumor Clinic. Mount Auburn Hospital, Cambridge.
*4:00–5:00 p.m. Child Psychiatry. Burnham Memorial Hospital for Children (Burnham 4), Massachusetts General Hospital.
*4:00–10:00 p.m. Alcoholism Clinic. By appointment. Washingtonian Hospital, 41 Waltham Street.

SATURDAY, JANUARY 22

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*8:00–9:00 a.m. Anesthesia Conference. Dr. Etten. Pratt Lecture Hall, Joseph H. Pratt Diagnostic Hospital.
*8:30–10:00 a.m. Orthopedic Staff Conference. Boston City Hospital.
*9:00–10:30 a.m. Surgical Grand Rounds. Dr. Child and Staff. Stearns Auditorium, New England Center Hospital.

(Concluded on page xxxii)